SCIENTIFIC PROCEEDINGS OF THE TWENTY-SEVENTH ANNUAL MEETING OF THE AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS

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AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS

A Comparative Study of Basic Beef Heart Antigens in the Wassermann Test. Marjorie C. Albray (by invitation) and L. W. Famulener, New York City.

Abstract. Eleven antigens were prepared by various recognized methods from each of a number of fresh beef hearts. Comparative tests, to determine (*a*) relative hemolytic activities; (*b*) anticomplementary properties and (*c*) antigenic values, were carried out for each series.

The preliminary studies as reported were summarized as follows:

(*a*) *Hemolytic bodies.* The Noguchi acetone-insoluble antigen prepared by the *old method* and the Kahn antigen showed the least amount of hemolytic bodies, the Kolmer antigen, a slightly higher content, while the Noguchi acetone-insoluble antigen prepared by the *new method* showed a higher content, but not to a marked degree. The simple alcoholic extract antigen showed quite a high content of hemolyzing bodies. The addition or omission of cholesterol did not noticeably influence the degree of hemolysis in parallel tests.

(*b*) *Anticomplementary substances.* The Noguchi acetone-insoluble antigen, prepared by the *old method* averaged a slightly higher content of these bodies than the Kolmer or the Kahn products. The simple alcoholic extract antigen showed the least amount, but perhaps this factor was masked by the higher content of hemolytic substances present.

(*c*) *Antigenic values.* In each instance, the Noguchi acetone-insoluble antigen, prepared by the *old* or the *new* methods, showed the highest values (unit strength). Both occasionally showed a higher value when cholesterinized. The Kolmer antigen approached the Noguchi antigens rather closely in some instances, but the average values were less. The Kahn antigens were somewhat lower in value and in general paralleled the cholesterol content when this was varied, but not always (one exception). In general, the Noguchi and the simple alcoholic extract antigens did not show any decided increase in antigenic values on the addition of cholesterol (0.2 per cent) although exceptions occurred.

These studies are being continued with the hope of further elucidation of the question.

(*No discussion.*)

The Absorption of the Toxic Substance of Normal Goat Serum by Guinea Pig Tissue. J. D. Aronson, Philadelphia, Pa.

(*Abstract not received.*)

Local Hypersensitiveness. L. Dienes, Asheville, N. C.

(*Abstract not received.*)

Studies on the Absorption of Unaltered Protein. Matthew Walzer, New York City.

(*Abstract not received.*)

DERMAL TESTING AS AN AID TO DIAGNOSIS OF INTESTINAL PARASITIC INFESTATION. Matthew Brunner (by invitation), Albany, N. Y.
(*Abstract not received.*)

STUDIES OF ATTENUATION AND OF TOXIC PRODUCTION OF THE DIPHTHERIA BACILLUS. Mary W. Wheeler (by invitation), Albany, N. Y.

Abstract. These studies of attenuation of the diphtheria bacillus and its toxin production in synthetic media brought out certain interesting facts. One of six subcultures of the standard Park No. 8 strain of the diphtheria bacillus grew in Uschinsky's medium. This culture was avirulent and non-toxic and these properties could not be reëstablished. Agglutination and absorption reactions alone gave evidence that the strain was closely related to the original Park No. 8 strain. More than fifty subcultures of the standard strain and thirty other strains failed to grow in Uschinsky's medium.

Growth and toxin production of the standard strain was obtained in synthetic media containing the chlorides, sulphates and phosphates of sodium, calcium and magnesium with dextrose as the source of energy and peptone as the source of nitrogen. No growth occurred if purified serum albumin or fibrin, pseudoglobulin, primary or secondary albumoses, purified peptone, asparagin, histidine or glycocoll were substituted for the peptone.

In the medium containing only peptone and inorganic constituents, a reaction of pH 7.4 to 7.6 and the presence of 0.2 per cent dextrose was most favorable for growth and toxin production. It was interesting to note that a potent toxin was produced only when the medium contained calcium and phosphate ions heated together in the presence of peptone. In the preparation of a medium with a peptone with high calcium content, the addition of other calcium salts was unnecessary. If, however, such a peptone was rendered free from calcium, it was necessary to add other calcium salts. The calcium ions could be replaced by equivalent amounts of barium or strontium, but not by magnesium or manganese. The addition of colloidal calcium phosphate to a medium which was unfavorable for toxin production, stimulated toxin production, but the potency of toxins from which the calcium was precipitated was unaltered. No significant differences were observed in the nitrogen metabolism of toxic and non-toxic filtrates of cultures of the standard strain grown in a medium of exactly the same chemical composition.

Discussion

(Dr. F. M. Huntoon, Glenolden, Pa.) I wish to congratulate Miss Wheeler on her paper. The production of diphtheria toxin has caused much difference of opinion because every producer has had his own ideas and theories particularly about the question of leaving the muscle-sugar in or removing it. It was felt that the production of diphtheria toxin was an art and each worker felt that his method was the only authentic method. Now Miss Wheeler has shown that it may be produced in peptone water if conditions are controlled. This work has aided very considerably the well-being of the diphtheria toxin products.

(Dr. I. S. Falk, Chicago.) I would like to ask how long it takes for the toxin to appear and the earliest stage at which potent toxin can be obtained.

(Dr. B. Steinberg, Toledo.) We had some experience in trying to produce soluble toxins and found that the nature of the media, the pH and the presence of sodium salts made a great deal of difference. This paper explains a good many things to me.

(Dr. A. B. Wadsworth, Albany.) In addition to the fundamental observations on the conditions underlying toxin production, I think it is also interesting to point out, in this study of the attenuation of diphtheria bacilli, that the practically non-virulent strains could not be rehabilitated. Similar observations have been made on the pneumococcus with the attenuated strains that came from horses undergoing immunization. In the recent study of these strains, it was found that after a certain stage of attenuation the rehabilitation of the virulent type of culture is apparently extremely difficult, in fact, it was not accomplished in the experiments which were made.

(Dr. H. Zinsser, Boston.) I should like to ask Miss Wheeler whether in the attempt to rehabilitate the colony, her observations in any way corresponded to rough and smooth differences. This has just been discussed in the English Journal of Pathology. Has Miss Wheeler any observations which indicate that the non-virulent rough strains could be brought back to smooth? This is a condition which we have never succeeded in bringing about in our laboratory but which is quite commonly reported in the literature by others.

(Miss M. Wheeler, closing.) In reply to the question as to when the toxin appears: With the small quantities of medium used in most of these experiments, 15 cc., a potent toxin was present in from 24 to 48 hours.

At the time the experiments were made with the attenuated strain growing in Uschinsky's medium, no particular note was made as to whether this strain produced rough or smooth colonies. Colony formation, however, was not typical and I should say the colonies were rather hard and dry. Morphologically, the organisms were not typical but were very short and coccoid.

ACTIVE IMMUNIZATION AGAINST EXPERIMENTAL PERITONITIS. Bernhardt Steinberg and Harry Goldblatt, Cleveland, O.

Abstract. It has been shown in previous communications that following injection of colon bacilli suspended in physiologic salt solution, into the peritoneal cavity of dogs, these animals survived and at the same time showed a bacteremia. However, when colon bacilli were suspended in gum tragacanth and injected intraperitoneally the animals died but no bacteria were found in the circulation. It was postulated that death was due to absorption of toxic substances. The present communication is an indirect evidence of that assumption.

Dogs were immunized with small doses of living and killed colon bacilli. After varying intervals subsequent to the last immunizing dose, the dogs were given a lethal injection of gum tragacanth and colon bacilli. All the immunized animals survived.

Experimental peritonitis was produced by intraperitoneal injection of fecal material into dogs. A large number of dogs immunized with colon bacilli survived the injection of fecal material into the peritoneal cavity, while all the control non-immunized dogs died.

(*No discussion.*)

IMMUNIZATION OF HORSES TO ERYSIPELAS STREPTOCOCCUS TOXIN. John F. Anderson and (by invitation) George F. Leonard, New Brunswick, N. J.

Abstract. The results of the immunization of a group of horses with strains of erysipelas streptococci isolated by Dr. Konrad E. Birkhaug are reported. Using a combination of the injection of toxin from these strains of streptococci and the blood clot method of immunization, the horses have been bled for produc-

tion in an average period of three months. Their plasma contained more than 5000 neutralizing skin test doses of antitoxin per cubic centimeter. The use of this antitoxin in a series of cases of erysipelas was followed by a rapid decline in temperature, pulse and respiration, and disappearance and fading of the erysipelas lesions.

Discussion

(Dr. A. B. Wadsworth, Albany.) What was the virulence of the culture? You spoke of their being extremely virulent, how virulent?

(Dr. J. F. Anderson, closing.) I should have used the word toxic, extremely toxic, I judge by the toxin produced.

THE INCIDENCE OF VARIOUS SPECIES OF BACTERIA IN SPECIMENS OF SPINAL FLUID FROM CASES OF MENINGITIS. Ruth Gilbert and (by invitation) Marion B. Coleman, Albany, N. Y.

Abstract. In a bacteriologic study of 284 specimens of spinal fluid received since Jan. 1, 1920, from cases of meningitis occurring in New York State outside of New York City, only eighteen strains of meningococci were isolated. Three of these corresponded serologically to Gordon Type I, and three to Type II; one agglutinated equally well in Types II and III sera, and one in all three sera. The others were atypical strains.

The number of tuberculous spinal fluids was relatively very high, amounting to 167. Eighty-nine of the patients from whom these specimens were submitted were under 10 years of age.

Pfeiffer's bacilli were found in 23 cases, pneumococci in 33, and streptococci in 35; and in 8 instances organisms not commonly associated with meningitis were present.

It is important to note the relatively low incidence of meningococci in this series, which is even lower than that of *B. influenzae*. As the mortality in cases of meningitis due to *B. influenzae* is very high and there is some evidence that vaccine or serum treatment might be of value, a further study of such agents may be indicated.

Discussion

(Dr. H. Zinsser, Boston.) We have been studying immunization by the blood clot method during the last few years. The work that Dr. Lawson has done is very definite but not quite completed. I am rather surprised by the fact that the older studies of the influenza bacillus and the sub-groups do not seem to hold good in the studies we have made of the influenza bacillus which we have isolated during the last two years in Boston.

(Miss R. Gilbert, closing.) Those that we have isolated have not been definitely typed but we have most of them and the study can be continued.

SIPHONIC FERMENTATION TUBE FOR THE MORE RAPID ISOLATION OF THE COLON-TYPHOID GROUP OF ORGANISMS. F. B. Jones (by invitation), Montreal, Can.

Abstract. This siphonic tube was invented with the idea of reducing the time that is usually consumed in the growing and detection of these organisms. It consists of two glass bulbs which act as reservoirs and receive the fluid as it is displaced from the siphon by the collection of the gas produced during the proc-

ess of fermentation of the sugar. These bulbs are connected by an intervening siphon which consists of glass tubing of small caliber and is bent in the form of an inverted "V." As the gas is produced it readily collects in the acute angle of this inverted "V" and breaks off the direct communication, through the fluid, between the two glass bulbs.

This tube may be used as a fermentation tube generally wherever it may be found necessary to use such a tube.

(*No discussion.*)

THE FIRST ANNUAL REPORT OF THE REGISTRY OF TUMORS OF THE LYMPHATIC SYSTEM. G. R. Callender and J. F. Coupal, Washington, D. C.

Abstract. Forty-two tumors tentatively classified as shown in the following table have been received by the registry.

Tumor Registry, 1927

Tuberculosis			1
Hyperplasia in Lymph Nodes, Generalized			2
Lymphosarcoma	Plasma cell type	1	4
	With terminal leukemia	1	
	Typical	2	
Reticulum cell, malignant	Localized	1	6
	Diffuse	5	
"Hodgkin's Disease"	Typical	6	14
	Mixed cell	1	
	Sclerosing	5	
	Large cell	2	
Lymphatic Leukemia			7
Chloroma	Lymphatic Leukemia	1	2
	Myelogenous Leukemia	1	
Hyperplasia, Erythrogenetic tissue (Infant)			1
Carcinoma	Lung	3	5
	Testicle	1	
	Squamous cell	1	
TOTAL			42

A classification of these tumors based on histogenesis is presented for discussion. A schematic outline of this classification is shown below. Pathologists were urged to send in samples of tumors of this kind for registration wherever it was possible for them to get the necessary data together, without reference to the person referring the case, it being understood that such cases were only available for study, and would not be reported without the consent of the pathologist registering them.

Discussion

(Dr. S. B. Wolbach, Boston.) I would like to ask Dr. Callender which vital stains he would like employed.

(Dr. Callender.) As I have done no work with the vital stains in this group of tumors I am not competent to suggest just which of the dyes should be used in the study. Janus green and brilliant cresyl blue have both been used, the former immediately on removal and the latter by injection before operation.

The clue perhaps to the method of study is contained in the rather numerous papers that have been written on the endothelial leucocyte or histiocyte.

(Dr. Wolbach.) Don't you think it would be advisable to advise a uniform technic? For your Council to state which vital stain or supra-vital stain would be best?

(Dr. Callender.) I do not think we are prepared to establish a uniform technic for vital staining but would refer that question to the Committee, Drs. Mallory and Ewing, for reply.

(Dr. James Ewing, New York.) Any good staining methods are all right.

(Dr. A. Plaut, New York.) Dr. Callender raised the question of erythroblastoma. Ribbert has published one case. Diffuse erythroblastosis seems to occur only in the newborn and I wonder if it belongs directly to the diseases which have been grouped here. Congenital erythroblastosis is an extreme exaggeration of the red blood picture present in the newborn. It is connected either with jaundice or severe congenital hydrops.

(Dr. Callender.) It was not my intention to call that a tumor, but just to point it out.

(Dr. Plaut.) In speaking about tumors, I only referred to Ribbert's case.

(Dr. Ewing.) I have been over all these cases and I am convinced that the registry is of value. I have learned a great deal from the forty or fifty cases. One thing I think highly important and that is, so far as possible, to have the bacteriologic studies. Several of these cases were very important bacteriologically. As for stains, every man has his own specialties in this field, and well fixed material stained by any method that is capable of analysis is the essential thing. Many of the specimens were not very well fixed. Bacteriologic studies and very thorough fixation of tissues seem the most important desiderata.

EXPERIMENTS OF TWO YEARS ON THE RELATION OF HODGKIN'S DISEASE AND THE ORGANISM ISOLATED BY GRUMBACH. Herbert Fox, Philadelphia, Pa.

Abstract. Some observations upon the relationship of diphtheroids to Hodgkin's disease and their pathogenicity, the occurrence of the lymphogranuloma in the lower mammals especially primates, and the blood picture of rhesus macacs are reported.

Repeated injections of the diphtheroid isolated by Grumbach from the blood stream of Hodgkin's disease during its active phase, into non-tuberculous rhesus macacs, during two years failed to produce in these animals any lesion that, grossly or minutely, resembled Hodgkin's disease. Injection of these cultures into guinea pigs confirmed in part Grumbach's work but it does not seem to the writer that the lesion in the lungs or lymphatic tissue should be called lymphogranuloma. With the monkeys the method was based upon the repeated introduction of large numbers of the bacteria so that constant assault upon the lymphatic tissue would exist. That the organisms were present in the body of the monkeys was indicated by the fact that No. 2 animal when sacrificed two months after the last dose, had the bacteria in the heart's blood.

Observations of the two animals during two years, and of the tissues, blood and serum of one of them at death fails to reveal any specific pathology indicating pathogenicity of the diphtheroid. The only and important specific reaction was a small amount of agglutinin. No complement fixation amboceptor appeared.

Hodgkin's disease has not been observed in the 3,000 mammals and 5,000

birds at this laboratory. Study of the lymphatic and myeloid tissues of primates indicates that the anatomic basis for the disease is as available as in man. Examination from an etiologic standpoint leads nowhere because it begins nowhere. The cases in domestic animals as reported in the literature are not convincing and are usually sarcoma or leukemia. The more acceptable cases might be myeloid hyperplasias dependent upon anemia.

It is not safe at present to attempt to state a normal blood count of the rhesus macac. There are variations due to factors not yet understood. It is best to determine the normal variations of each experimental macac and establish his own modes. Hemoglobin and red cells vary with the health of the beast and tend to rise after the animal comes from the dealers and becomes accustomed to new surroundings and gets good food. Repeated handling may affect the blood count; it certainly makes the temperature higher.

Leucocytes vary from 5,000 to 25,000 with an average of 10,000 to 13,000. Neutrophiles are the most numerous individual cell, having a percentage average of 44 to 54 per cent. Lymphocytes are next, their average being 33 to 47 per cent. Eosinophils and basophils are extremely variable and this work revealed no mode nor any reason for the variation. Many cells comparable to neutrophilic polynuclears have fine basophilic granulations. Mononuclears average 5 to 6 per cent. The leucocytes are not greatly affected by food. Sometimes the number drops, sometimes rises, after a meal following a fast.

The leucocytes of rhesus macacs perform a daily cycle of numbers with a high peak in the late evening hours. The course during the day hours is irregular but fails to show a distinct rhythm. The lowest counts seem to be from 11 A.M. to 3 P.M. The late evening rise is due chiefly to polynuclears. The leucocytes rise in numbers while the temperature is performing its normal night drop. This daily rhythm occurs without relation to food or sleep.

(*Discussed with next paper.*)

RELATION OF POLYNUCLEAR NEUTROPHILES AND THEIR REACTION TO X-RAY, TO CERTAIN LYMPHADENOPATHIES. Herbert Fox, Philadelphia, Pa.

Abstract. From the evidence here collected the leukemic group is composed of true chronic lymphatic leukemia, sublymphatic leukemia and leucosarcoma in that they have, with lymphocytosis, a low number of neutrophiles which are very susceptible to radiation treatment. Aleukemic lymphadenosis tends to have the percentages and numbers of neutrophiles and lymphocytes approach normal with relative insusceptibility to radiation. The cases have a tendency to caseous involvement, which is, however, not in our two cases attended by polynucleosis, and therefore suggest myelomas which are not characterized by a peculiar blood picture. This group of adenoses resembles somewhat in hematology lymphosarcomas. The tendency to final malignant stages as evidenced by the bony tumors in adenosis, increases the resemblance. The neutrophiles in lymphosarcoma do not fall consistently under radiation.

Hodgkin's disease is marked by a polynucleosis which is indifferent to radiation except in the malignant and febrile cases when these cells are quite variable. Our single cases of reticulum cell sarcoma and endothelioma had neutrophiles unaffected by radiation and of no definite numbers.

From these figures then, one can deduce that there is a leukemic group — true chronic leukemia, sublymphatic leukemia and leucosarcoma, and a sarcoma group — aleukemic lymphadenosis and lymphosarcoma, with distinct neutro-

phile picture and reaction to radiation. These are separate from Hodgkin's disease which varies with its type and from endothelioma and reticulum cell sarcoma. These features, if corroborated with a biopsy, will somewhat simplify the classification of a given case.

Discussion

(Dr. E. B. Krumbhaar, Philadelphia.) I think it well worth while to emphasize the normal variations in the blood picture of any animal. Probably this is more noticeable in the monkey than in other laboratory animals. However, I feel that that should not prevent an attempt to draw deductions from hematologic studies if extra precautions are taken to standardize the counts in every way possible. If the same individual use the same pipette at the same time of day under conditions that are practically constant, many of these fluctuations will be minimized to a point where the results will be useful.

(Dr. B. Steinberg, Toledo.) A few weeks ago I had the opportunity to run through a series of twelve dogs. We had taken the temperature at two hour intervals, leucocyte counts, etc., and it was surprising to find how they varied. The temperature varied from 96° F. to 100° F. and the leucocytes from 4,000 to 12,000 in apparently normal dogs. We therefore could not find any normal standard to make out further experiments because of this variation in temperature and leucocyte counts.

(Dr. James Ewing, New York.) We have in our museum a uterus which was removed some years ago from a dog. The endometrium is about one-half an inch thick. I called this Hodgkin's disease but whether genuine or not I do not know. It has the histology and the gross anatomy of Hodgkin's disease.

(Dr. H. Zinsser, Boston.) I would like to say that in the case of rabbits a sort of fluctuation of the leucocyte count and the temperature appears but if one follows it consistently for long periods one can get departures from the normal. As far as diphtheroids of Hodgkin's or of any other disease, I do not think any bacteriologist who is familiar with diphtheroids pays any attention to an etiologic claim for a diphtheroid unless there is absolutely overwhelming proof.

(Dr. J. F. Coupal, Washington.) This paper brings out quite prominently the importance of quantitative studies of radiation in the Registry records as well as the value of the white counts. We do not need to annoy the clinicians too greatly about the history as long as we get the quantitative and qualitative record of the amount of X-ray and radium used.

(Dr. E. B. Krumbhaar, Philadelphia.) It would be interesting to know where significant changes had taken place and whether the polymorphonuclears in the young or old forms had been increased or decreased. I might take this opportunity to urge that a slight modification of the differential count will permit one to divide the polymorphonuclears into the old and young forms by a consideration of the nucleus and a very occasional metamyelocyte, so that the time for doing the differential count is only added to by five or ten minutes. In one case of low grade chronic lymphatic leukemia I made for several weeks an Arneth's formula and there appeared a constant reduction, the curve shifting rather to the right.

INTRA-VITAL STAINING AND PHAGOCYTOSIS IN HOGDKIN'S DISEASE, LEUKEMIA AND SARCOMA. Herbert Fox, Philadelphia, Pa.

(Abstract not received.)

ACUTE LEUKEMIA WITH EXTRA MEDULLARY MYELOID CENTERS. Harry T. Marshall and (by invitation) Katherine Woodward, University, Va.

Abstract. A negro child of five, after acute infections repeated over three months, died with features of acute leukemia and pronounced anemia. Pneumococcus on blood culture at necropsy.

The kidneys showed nodules, bright red in color like infarcts. Similar red splotches on dura mater. Malpighian hyperplasia in spleen. Pneumonia, organizing. No general glandular enlargement. Pansinusitis.

Microscopically, the red splotches in dura and kidney were not infarcts, hemorrhages or leukemic infiltrations. They were myeloid centers. Similar changes appeared in lung and to a less degree in peribronchial lymph nodes.

Conclusions are drawn as to the scope of the term "acute leukemia"; its applicability to this case, and its nature. The relation of findings to the definition of lymphocytes is indicated. Suggestions are made as to the bearing of this case upon current views of blood formation.

NOTE: Dr. Marshall defined tumor and leukemia before beginning his paper.

Discussion

(Dr. James Ewing, New York.) Did you find any traces of hemoglobin in these cells?

(Dr. Marshall.) Oh, yes.

(Dr. Ewing.) You didn't mention it.

(Dr. Marshall.) In the early picture the cells had distinct hemoglobin at all stages of hemoglobin formation from a deep basic cytoplasm, to the cells in the kidney interstices and lung interstices with various stages of hemoglobin.

(Dr. A. S. Warthin, Ann Arbor.) Did you examine the periosteum for similar cells?

(Dr. Marshall, closing.) No.

GENERALIZED RETICULAR-CELL SARCOMA OF LYMPH NODES, ASSOCIATED WITH LYMPHATIC LEUKEMIA. Maurice N. Richter, New York City.

Abstract. The purpose of this communication is to report a case in which a generalized tumor of unusual type, apparently primary in the lymphatic system, was associated with the clinical, hematologic, and histopathologic features of lymphatic leukemia.

The patient was a man, 46 years of age, with marked enlargement of the superficial lymph nodes, spleen and liver. The duration of the disease was said to be seven weeks.

Blood examination showed 98,400 white cells per c.mm., of which 90 per cent were lymphocytes, mostly of the small variety.

Death occurred three weeks after admission. The clinical diagnosis was lymphatic leukemia.

Necropsy: B. H., No. 11643. Summary of positive findings.

Generalized lymphadenopathy. The abdominal nodes formed a retroperitoneal mass which extended from diaphragm to pelvis, and from spleen to right kidney. Cervical, axillary, inguinal, epitrochlear, mesenteric and thoracic nodes were also enlarged. The nodes were discrete, soft and measured from 0.1 to 8.0 cm. in diameter. Some were white or gray, some hemorrhagic in

whole or in part. In a few were central areas of the same consistence as the rest of the node, but of canary yellow color. None was necrotic.

Spleen: 23 × 15 × 10 cm. Surface nodular. On section there were numerous white, gray or yellowish circumscribed nodules scattered through the splenic substance. These nodules appeared to be of the same type as the enlarged nodes. The largest nodule was 2.0 cm. in diameter.

Liver: Enlarged. Weight 2,660 gm. There were numerous white, circumscribed areas similar to those in the spleen, but smaller.

Bone marrow (rib): Hyperplastic, grayish red.

Microscopic Examination: The lesions in the lymph nodes, spleen and liver are of two types: (1) Diffuse lymphoid hyperplasia and infiltration. (2) Multiple nodular and diffuse neoplasia of reticulum cells.

The first lesion is identical with that usually found in lymphatic leukemia.

The second lesion is in the form of large mononuclear, occasionally multinuclear cells of varying size, shape and arrangement. In some sections the arrangement is that of a sarcoma composed of fairly uniform cells; in others, the presence of giant cells causes a superficial resemblance to Hodgkin's disease. However, there is no necrosis, fibrosis, or eosinophilic infiltration.

Both lesions are present in the liver, spleen and all groups of lymph nodes examined. The lesions of leukemia and of tumor may be seen side by side, often with intermingling of their cells. The cells of each, however, maintain morphologic independence.

That the tumor is composed of connective tissue cells is evident, but the cell of origin is difficult to determine. However, a study of the sections indicates that the cells probably arise from the reticular cells of the lymphoid tissues, and there these cells form the boundary of lymphatic sinuses, from reticulo-endothelium, although they do not actively produce reticulum fibers.

The bone marrow shows replacement of the marrow cells by diffuse lymphoid tissue.

Discussion. The association of leukemia with a tumor suggests several possibilities of etiologic relationship. This is particularly true of this case because one of the lesions (the tumor) apparently arises from reticular and reticuloendothelial cells, which are thought to be potentially capable of producing blood cells of various types.

However, the cells of the tumor and of the leukemia, although closely intermingled, remain morphologically distinct, without transitions from one cell type to the other.

That the lymphoid lesion is a true leukemia, and not a "leukemoid reaction" to the presence of a tumor, is indicated by the typical histologic lesions of leukemia in the organs. Likewise, there is no direct evidence pointing to the dependence of the tumor on the presence of leukemia.

The lesions in this case can best be explained by regarding them as separate conditions which, although closely associated, are morphologically distinct.

Discussion

(Dr. A. S. Warthin, Ann Arbor.) I believe that Dr. Richter's neoplasm belongs to the same group as those that we have seen in our material and have called leukemic sarcomatous Hodgkin's or leukemic reticuloblastomas. Of twenty-nine cases of sarcomatous Hodgkin's twelve developed a leukemic transformation. These neoplasms are all genetically related. They all belong to the

same group as far as their pathogenesis is concerned and represent different degrees of differentiation.

(Dr. J. F. Coupal, Washington.) We have taken refuge in the Registry of the museum by looking upon the blood, not as a tissue like some of the older histologists did, but as an organ which helps in understanding the cellular pictures found in this type of case.

(Dr. G. R. Callender, Washington.) I hope nobody who has a case approaching this in interest will avoid the Registry.

(Dr. A. M. Pappenheimer, New York.) I had the privilege of studying these sections. On looking up our material at the Presbyterian Hospital for similar cases, we found five which showed an histology identical with the tumor part of Dr. Richter's case. None of our cases, however, was associated with a leukemic condition of the blood. This might indicate with Dr. Richter that the two processes are distinct.

(Dr. George Baehr, New York.) I should like to lay emphasis upon the fact that chronic lymphatic leukemia is often a very chronic disease which exists throughout a large part of the patient's lifetime. In such circumstances it may occasionally happen that the individual will develop some other type of neoplastic disease. We have observed two cases of primary carcinoma of the lung in patients with chronic lymphatic leukemia.

(Dr. M. N. Richter, closing.) With regard to the diagnosis of Hodgkin's in this case I do not think the section is typical of the usual type of Hodgkin's that we see, although the eosinophils are not essential. In examining a good many nodes from all parts of the body, and nodules from the spleen, liver and other organs I might hope to find an eosinophil occasionally, but I was unable to do so in any tissue examined. Another thing of importance is definitions of the various conditions that we are talking about. As we must rely on the histology for the diagnosis, we ought to know what we mean by the clinical terms "tumor" and "leukemia." I fail to find very good definitions of these conditions, particularly of tumors and I do not know how to tell whether leukemia is or is not a tumor without knowing what a tumor is.

DIFFUSE LYMPHOMA OF MESENTERY ASSOCIATED WITH CARCINOMA OF COLON.
Oscar T. Schultz, Chicago, Ill.

Abstract. In a man aged 54 years a mass was palpable in the left upper quadrant of the abdomen. The condition was believed to be an inoperable retroperitoneal sarcoma. Roentgen therapy was instituted, but had no detectable effect. Seventeen weeks after this admission symptoms of acute intestinal obstruction developed very suddenly. Colostomy was done. Death resulted from peritonitis three days later. At necropsy the entire mesentery was transformed into a layer of pale tissue 3 to 5 cm. thick, the liver and omentum were studded with carcinoma metastases, and an obstructing annular carcinoma was situated at the splenic flexure of the colon. The mass palpable during life was a portion of the thickened mesentery. The latter was free from carcinoma but had been transformed into a cellular tissue composed of closely placed lymphocytes. In places a follicular arrangement was present.

Discussion

(Dr. James Ewing, New York.) I would like to ask Dr. Warthin whether he thinks this is the same tumor condition.

(Dr. A. S. Warthin, Ann Arbor.) I do not think so.

(Dr. A. Plaut, New York.) I would like to ask how much fibrosis there was. One slide showed extensive fibrosis. Were there many spots like that?

(Dr. Schultz.) The section shown was from the periphery. There was not only no increase but a condensation of the bands of fibrous tissue near the surface.

(Dr. Plaut.) I asked for a special reason, because there was a condition of a tumor mass arising in the abdomen that was an "inflammatory tumor of the omentum," which Ewing has referred to as pseudosarcoma. A few years ago a case came into my hands and I found a large number of small foci of typical lymphoid tissue scattered throughout the extremely fibrosed omentum. There might be something similar in Dr. Schultz' case with the lymphoid tissue outgrowing the fibrous masses in the omentum. There must be some irritation but what kind of irritation seems to make little difference. This is only a suggestion.

(Dr. Schultz, closing.) In reply to Dr. Plaut I can only say that the striking thing was the diffuseness of the process; there were no nodules, but the entire mesentery and omentum were composed of a very cellular tissue of the structure of lymphadenoid tissue. There was no proliferative reaction whatever on the part of the stroma, and the lesion has none of the characters of a granuloma.

MALIGNANT LYMPH FOLLICLE HYPERPLASIA OF SPLEEN AND LYMPH NODES.

George Baehr and (by invitation) Nathan Rosenthal, New York City.

Abstract. A report of a study of six cases which represent a distinctive clinical and pathologic entity that can be differentiated from ordinary lymphosarcoma. The salient characteristics include: (1) lymphadenopathy due to hyperplasia of the germinal centers of the lymph follicles; (2) splenomegaly due chiefly to enormous enlargement of malpighian bodies, the weight of the spleen increasing up to 1,800 grams; (3) absence of abnormal cells in the blood; (4) absence of anemia or cachexia; (5) tendency to development of serous effusions in the pleural and peritoneal cavities due to the pressure of mediastinal or abdominal lymph nodes upon venous or lymph vessels; (6) absence of involvement of tonsils and lymphatic apparatus of the gastro-intestinal tract; (7) tendency to lymphatic infiltration in lacrymal gland resulting in unilateral exophthalmos. Aside from the absence of anemia and cachexia, the chief differential feature distinguishing the condition from lymphosarcoma is its origin multicentrically throughout the body in the lymph follicles, whereas lymphosarcoma arises monocentrically and spreads by lymphatic extension. Both lymph node and splenic enlargements respond with remarkable promptness to X-ray or radium therapy.

Discussion

(Dr. G. R. Callender, Washington.) We have two cases quite similar in the registry, one of which we followed for six years. Sometimes an overdose of X-ray gives rise to serious clinical symptoms.

(Dr. Baehr, closing.) I shall be glad to accept the correction as to terminology for there are undoubtedly more follicles in the spleen than are normally present,

but the malpighian bodies which normally are present are tremendously hyperplastic and although small collections of lymphocytes may have developed into additional follicles, I am at a loss to know what else one could call the condition except malignant lymph follicle hyperplasia. As to the caution about use of the X-ray, we have also records of a case which was treated with radium by someone else. The treatment was kept up long after the evidence of lymphatic involvement had disappeared, until eventually the patient developed a profound anemia and other evidences of radium poisoning.

THE NEOPLASTIC RELATIONSHIP OF HODGKIN'S DISEASE, ALEUKEMIC AND LEUKEMIC LYMPHOBLASTOMAS AND MYCOSIS FUNGOIDES. Alfred S. Warthin, Ann Arbor, Mich.

Abstract (not received).

Discussion

(Dr. H. Zinsser, Boston.) I wonder if Dr. Warthin knows how that sounds to a bacteriologist. It sounds like a catalogue of the ships in the second book of Homer. Perhaps Dr. Ewing may have some comments.

(Dr. James Ewing, New York.) I remember, Dr. Warthin, that paper which you presented in the early nineties. My criticism of the conclusions, I think, on the whole, was justified by the manner in which you yourself, just now, tore the entire classification to pieces. The only thing you left was the first term in the classification, "lymphoblastoma" and that I would demolish, as you do not seem to have the courage to do, by expressing the belief that there is no such thing as a parent cell of all these various neoplasms. I confess that Dr. Warthin's enormous material, which he has worked up for so many years with great care, may justify him in his rather firm and dogmatic opinions. However, I think Dr. Mallory could duplicate the numbers and possibly many of the varieties. Modesty prevents me from telling what we might show at Bellevue and New York and I think that Chicago could go a long way, so that on the whole one might encounter equally dogmatic opinions drawn from almost the same amount of material in many cities. This encourages me to retain some of my own notions about the subject which are not nearly as clear or as positive as Dr. Warthin's. The main ground for dissatisfaction with his Table is that in 1897 he proposed one name for this entire group of lymphoid reactions and he holds that opinion still. I think that is not going to help us much. I believe that as long as the etiologic factor or factors are missing, either bacterial, toxic or neoplastic, the only way of making real progress is to adhere closely to the morphologic distinctions in the hope that some day we shall find different specific agents associated with these pictures. It is my firm belief that that will be the outcome. I do not believe it is wise to assume that all leukemic processes are neoplastic or spontaneous non-altruistic growths. I believe many of them have distinct relations to infections. I have seen leukemic processes develop from pneumonia, acute tonsillitis and diphtheria and run a short and fatal course, or run a longer course into chronic leukemia. I think it entirely different from Hodgkin's disease which to my mind bears all the marks of a specific infectious disease. Although we may not be able to find clear differences in all cases, how are we going to make progress by throwing them all into one category? I would rather see the most minute differences emphasized and a classification based upon them until the time when the etiologic factors unify or subdivide the entire group.

(Dr. Zinsser.) I think it is almost my duty to ask Dr. Mallory whether he has anything to say.

(Dr. F. B. Mallory, Boston.) I shall be sufficiently destructive in the next paper so I shall refrain now.

(Dr. H. T. Marshall, University, Va.) In regard to one or two of these pictures that were shown which resemble the picture that I found in the infant, I was able to see indications of actual activity in the elongated cells between the renal epithelium, not within the tumor but in the new growth occurring between, which would not be tumor in the sense described by Dr. Warthin. Moreover, like Dr. Ewing I feel that Dr. Warthin has failed to take account perhaps of the adaptive changes that lymph nodes are capable of exhibiting. The only way to get any result would seem to me to be a tabulated series, studying the known irritants in measurable gradients. I think you will find that many of the changes are reactions in the nature of inflammatory adaptation.

(Dr. M. N. Richter, New York.) Now that we have definitions of the conditions which we are discussing I think perhaps we are in a position to talk of the etiology and the pathogenesis. I am particularly interested in the various blood pictures resembling leukemia. We know that various tumors metastasizing to bone marrow might throw out bone marrow cells into the circulation. I wonder whether the metastases to lymph nodes would not throw out various lymphocytes by a mechanical process without the necessity of assuming a separate neoplasm for their appearance in the blood. I would like to ask, in tumors associated with myeloid leukemia, what picture the bone marrow showed. Whether, for example, Hodgkin's in the bone marrow might possibly account for the irritation and the outpouring of myeloid cells.

(Dr. J. F. Coupal, Washington.) I think if we reiterate that these tumors arise from the various portions of the reticulo-endothelial system considered rather as an organ than as a tissue, we can justify all of Dr. Warthin's paper. If we remember that their stages of reversion proceed back to the primitive form, the embryoma, we can understand why these tumors exhibit so many cellular variations. The tendency for these tumors to form after chronic inflammation of this system, especially in its grosser lymphatics, indicates that it is subsequent to hyperplasia and hyperfunction rather than irritation and structural defects usually the cause of tumors in other organs. In addition, this system has repeated calls for a massive increase of physiologic action, as the rapid formation of large numbers of leucocytes and the vast increase in function shown in swelling of the lymphatics consequent upon infection. These marked variations of amplitude of function correspond to the marked, periodical, physiologic variations that occur in the breast and uterus, and which expose them to their high incidence of tumor.

(Dr. Zinsser.) I venture into this discussion reluctantly but I have been rather surprised by the frequent reference to the infectious origin which has been mentioned. This in particular applies to Dr. Ewing's reference in regard to Hodgkin's disease. I have been associated with some of the studies indirectly with Dr. W. C. Clark in which two chimpanzees observed by complement fixation reactions and bacteriologic studies were innoculated directly in the upper arm with Hodgkin's material under accurate control for many months. These experiments were completely negative. As a bacteriologist, I no longer have any confidence in the infectious origin of Hodgkin's disease.

(Dr. A. S. Warthin, closing.) I should like to lay out my old friend Ewing completely but I have great hopes for him. He will be something more than a

fundamentalist yet, I am sure. I will say that about the same time I was interested in the heredity of cancer he treated that idea even more roughly, but even now in his own book there are suggestions of an awakening belief concerning the heredity of neoplasms. We have exactly the same situation here, in the case of the lymphoblastomatous growths, Hodgkin's disease and mycosis fungoides, that we see in the case of other neoplasms. There is a great deal of evidence as to the intrinsic nature of these conditions, particularly with reference to the family history and the family incidence, three or four cases occurring in the same family in one or different generations, and I believe the problem here is essentially that of neoplasm in general, a genetic problem. The etiology is a problem of the germ cells and the qualities contained in them. As to infections of various kinds playing any part in the etiology of this group there may be some non-specific exogenous factor that will bring out the inheritable constitutional susceptibility but these processes do not in any way conform to infections. There is no inflammation in these neoplasms except occasionally a very slight secondary one. I think the spindle cells you saw in the slides are simply flattened cells. All of the patients are dead. The course of these affections is inevitably fatal, but the fatal issue may be prolonged by irradiation. These diseases spread by infiltration; they are all essentially destructive; they have no protective function; they have all the characteristics of neoplasms and none of an infectious process. They all represent neoplastic overgrowths of the parent tissues of the blood cell forming reticulo-endothelium or endothelium and differ only in degree of differentiation.

RETICULUM. F. B. Mallory and Frederic Parker, Jr., Boston, Mass.
(See page 517.)

MENSTRUATING UMBILICAL TUMORS. Carl V. Weller, Ann Arbor, Mich.

Abstract. Two umbilical tumors presenting all the characteristics of the so-called umbilical adenomyomas have been recognized in the Department of Pathology of the University of Michigan. One of these occurred in a woman 49 years old, while the other patient was 45. In the first case there was bleeding from a small nodular umbilical tumor at each menstrual period. In the second case, only histologic evidence of menstruation was available. These tumors showed the characteristic endometrial structure in respect to both glandular elements and surrounding cellular stroma but no smooth muscle belonging to the tumor was found in either instance. The absence of such muscle has been mentioned in other reported cases and the term "adenomyoma" is, therefore, a misnomer. Greater importance is attached to these tumors from the standpoint of the evidence which they afford as to the histogenesis of this group than to their clinical aspects. Of the latter, the most important is recognition of the fact that they are neither primary melanoblastomas nor metastases of malignant intra-abdominal neoplasms, conditions with which they are usually confused clinically. As to histogenesis, the occurrence of this tumor at the umbilicus cannot be satisfactorily explained as being due to endometrial implantation or to lymphagenous or hematogenous metastasis from proliferating endometrial growths in the pelvis. It throws doubt upon the theories of Sampson in regard to the origin of this entire group and seems to find its best explanation in a theory based upon a serosal origin.

Discussion

(Dr. A. Plaut, New York.) I would like to ask Dr. Weller and others as well, whether from this picture there was created an impression of a true neoplasm. I have the impression that these are not neoplasms. They are not circumscribed, not adenomyoma, but diffuse lesions. These glandular ducts which we have seen look really perfectly normal. They do not show signs of autonomous growth and the idea that such tissue should metastasize, I do not think, would occur to any of us in looking at slides of this character. As to the question of origin, I personally do not favor the theory of Sampson but rather the peritoneal theory which, I think, in some cases has been proven. But there is another possibility to be considered; these glandular ducts might be transformed lymph vessels, these epithelial cells might originate from endothelial cells. I fully realize what a shock this might cause to some tissue workers. I have seen a number of slides which led me to think of this possibility. Later I saw the excellent photomicrographs in the paper by Schiller in Vienna who comes to the same conclusion. If this theory is true, it can help us in understanding the diffuse multicentral character of adenomyotic lesions. If they are metastatic or embolic then we must assume that they migrate extensively in spite of their showing no signs of autonomous growth. On the other hand, the transformation of flat endothelial cells into higher columnar epithelial cells at several points in the same organ under the same stimulus seems to offer less difficulties of explanation.

(Dr. A. S. Warthin, Ann Arbor.) Have you ever found anything like this in the male?

(Dr. Plaut.) No, only in females where we can assume the activity of the female sex glands. Never before puberty and never more than a few years after menstruation ceased.

(Dr. Warthin.) Why then, only in one sex?

(Dr. Plaut.) I cannot answer that, but observations have led others and me to this conclusion. I have even found in older books drawings which present the same thing but without the same interpretation, of course.

(Dr. V. C. Jacobson, Albany.) I fully agree that the lesion is not a tumor. I should call it ectopic endometriosis. In other words, there are normal appearing endometrial glands plus normal stroma which at each menstrual period menstruate. I cannot conceive of strictly neoplastic tissue adhering to a normal function in such a normal way. As to why it is found in the region of the umbilicus I think the explanation in many of these cases lies in the fact that there are small umbilical hernia sacs present. Recently, I had the opportunity of studying a menstruating mass in the sac of an umbilical hernia. Endometrial tissue which had been set free in the uterine cavity had found its way into this sac. The endometrium fragments discharged at menstruation from the tubes or more often from ruptured endometrial cysts in the ovary wander around and find their way into certain places where they become anchored. The most important point in all this discussion lies in determining whether or not any of the endometrial cells cast loose at menstruation are alive. Novak and others feel that the tissue is all dead and if so Sampson's theory is wrong and Sampson's explanation just as dead. Dr. Sampson has shown (*Am. J. Path.*, March, 1927) that endometrial tissue can find its way into the uterine venous sinuses which are wide open during menstruation and a certain percentage of endometrial fragments become attached to endothelium and grow anew. They can in turn menstruate and give off more tissue which can be swept along even farther. I

think this article throws much doubt on Meyer's explanation of this condition. Another thing, if the peritoneal endometriosis is due to metaplasia of the peritoneal mesothelium why is it always or so frequently found on the under and lateral surfaces of the ovary and never on the anterior surface? The explanation probably lies in the fact that the fimbriated opening of the tube is on the under and lateral surface of the ovary. That is where the endometrial tissue is generally found. I should like to ask Dr. Weller if his patient had any menstruating ovarian cysts, or masses in either ovary. That is not necessary, however. In the case I have mentioned of menstruating endometrial tissue in the sac of an umbilical hernia, we searched the ovaries carefully and found no endometrial tissue. It was another instance of peritoneal implantation without any endometrial cysts in the ovaries which are usually responsible for this ectopic endometriosis. Many things are against the metaplasia theory. In the first place, it sounds very unreasonable to me to assume that such kaleidoscopic changes can take place in peritoneal mesothelium. The presence of menstruating cysts, the facts that the abdomen and particularly the pelvis contains menstrual blood and small masses of endometrium, and that these endometrial growths are usually found on the under and lateral surface of the ovary, point to peritoneal implantation of endometrial tissue. Also, I do not believe that the peritoneum forms decidua; the decidual cells are formed from the submesothelial fibroblasts.

(Dr. Weller, closing.) In the first place in regard to whether this growth is a true neoplasm or not: If this is not a neoplasm, a myoma is not a neoplasm. The fact that this neoplasm undergoes retrogression after sexual life is over is also true of a leiomyoma. In both of the cases described the neoplasm developed without trauma and there was no history of operation or of hernia. These neoplasms grow expansively. There is no limit to their growth until the age of sexual activity is over. So far as the origin and manner of growth is concerned these facts accord with many of the criteria for a true blastoma. The suggested possibility of implantation in an umbilical hernia does not help us very much. Why do such implants never get into the foramen of Winslow where there is a peritoneal pouch provided? There are many endometrial nooks and crannies which would correspond to an umbilical hernia. I do not believe that has anything to do with it. In regard to the continuity of these glandular structures, I am of the impression that they are independent structures. I have under way now a reconstruction which should settle that question. One of these neoplasms was removed nine years ago. As far as I can trace the history that patient did not subsequently develop ovarian cysts. My history of the case is not absolutely complete. In regard to the other case no internal pelvic examination was made.

SYNOVIOMATA: A HISTOLOGIC STUDY OF THREE TUMORS OF SYNOVIAL MEMBRANE ORIGIN. Lawrence W. Smith, Boston, Mass.

Abstract. Three tumors, occurring in relation to the knee-joint, and presenting too many points in common, both clinically and histologically, to be regarded as coincidental, are presented, as a type tumor to which no definite references can be found in the literature. Their histology, as based on their embryologic origin from mesothelium, is discussed. The type cell shows multipotential differential characteristics comparable to other mesothelial tumors, such as those arising from the pleura, pericardium and peritoneum.

Discussion

(Dr. A. S. Warthin, Ann Arbor.) Were these connected with any synovial cavity?

(Dr. S. B. Wolbach, Boston.) The third case was connected with the bursa beneath the patella. The other two cases developed in proximity to tendons.

(Dr. Jaffe.) Have you any idea of the frequency of these conditions?

(Dr. Wolbach.) These three cases and one other have come to our notice in about four years. One case Dr. Smith did not include in the series was sent to me from Vermont or New Hampshire. It received the same diagnosis and prognosis.

(Dr. V. C. Jacobson, Albany.) Have these any relation to the so-called xanthomatous tumors of tendon sheaths which contain many large cells filled with lipoid?

(Dr. Wolbach.) I do not know. Very probably a benign form. I become more and more convinced of what I frequently say to students that the so-called classification of tumors is simply matching tumors, about like what you do when your wife sends you down town to match a fabric.

(Dr. James Ewing, New York.) I believe these tumors represent a separate group, one of the common "rare" tumors. I found one recently which began well above the patella and I have seen one which was found in a long cyst in the middle of the thigh having the same general structure. I am sure it was of the same origin. I think there is evidence of a relation between these and the xanthomatous tumors which Dr. Jacobson mentions.

MALIGNANT MEDIASTINAL DERMOID WITH MENINGEAL METASTASIS. William F. Jacobs, Buffalo, N. Y.

Abstract. The number of mediastinal dermoids and teratoma reported in the last hundred years will approximate about one hundred cases. Of these, those definitely proved malignant will be about 10 per cent.

Carcinoma predominating and sarcoma next in order, two cases are reported of chorionepithelioma and two cases mixed, carcinoma and sarcoma.

The malignant change appears to occur not only in the solid teratoid growths, but also in the simple cystic dermoids.

Case report: A white adult male, 27 years of age; occupation — locomotive fireman. Complaint, — alleged fall, some fourteen weeks prior to decease when injury was received to left shoulder and chest, causing pain and shortness of breath; during final three weeks in hospital he developed signs of meningeal irritation, positive Kernigs with cervical rigidity. The spinal fluid showed increased globulin and a cell count of 34 with distinct web formation. The diagnosis at the time of death was pulmonary tuberculosis with secondary tuberculous meningitis.

Necropsy report: The body is that of a poorly nourished adult male, five feet eight inches, with weight estimated about 130 pounds, no signs of pulmonary arthropathy.

A tumor was found in the median line over the heart. It extended upward embracing the superior vena cava. The aorta was clear. The trachea and bifurcation formed the posterior part of the tumor. It measured 14 cm. in the vertical diameter, 8 cm. lateral and 8 cm. anteroposterior. On section it was found in part cystic and part solid. The cavity contained the usual sebaceous

material with hair. The inner wall presented a nodule from which the hairs were growing. The wall on section showed small areas of necrosis.

There was involvement of the peribronchial and paratracheal lymph nodes and the lower cervical group on the left side, also the lower pole of the left thyroid lobe.

The lungs, other than being markedly hyperemic, did not reveal any gross pathology.

The meningeal covering of the base and tips of the temporal lobes and its extensions into the Sylvian fissures were thickened, and presented numerous very fine granule-like nodules, suggesting tubercules.

The gastro-intestinal tract, liver, spleen, pancreas, kidneys, adrenals, prostate and testes were all negative.

Microscopic examination: The sections from different parts of the tumor mass revealed islands of hyaline cartilage, areas of striated muscle, smooth muscle, with a major portion made up of a dense hyalinized stroma, containing alveoli, more or less cystic with elongated columnar cells, suggesting respiratory mucous membrane. There are cystic areas lined by a very much modified stratified epithelium, showing both sudoriferous and sebaceous glands with hair follicles, and nerve fibers but no ganglian cells. The malignant phase of the tumor is represented by dense masses of adenomatous tissue in which the cells are small, cubical, at times showing considerable variability in size and chromatin content; the arrangement in the main exhibiting an attempt to form alveoli but often conforming to no order, showing no stroma, but being in solid masses, cords and strands; nowhere does there appear any limiting membrane; similar characteristics are found in the lymph nodes and thyroid.

In the lung sections, infiltration is found along the perivascular and peribronchial lymphatics. The infiltration extends directly through the vessel wall.

The involvement of the meninges was found to be in the form of strands or cords of cells resembling those of the primary tumor without special form or arrangement. They are generally found in close relation to the meningeal vessels with some few small round cells about them in the thickened meninges.

This case ordinarily would be classed with the simple cystic mediastinal dermoids. Histologically, however, we feel that it belongs to the teratoma.

Its malignant phase is represented by an adenocarcinoma, involving lymph nodes, thyroid, lungs and secondarily the meninges.

The factor of compensation, because of accident, prompted the postmortem examination.

The clinical diagnosis was pulmonary tuberculosis with secondary tuberculous meningitis.

The gross examination, while finding the primary tumor and immediate metastatic lesions, yielded a picture in the meninges that suggested tuberculous meningitis.

(*No discussion.*)

THE ENCAPSULATED TUMORS OF THE NERVOUS SYSTEM. (Meningeal fibroblastomas, perineurial fibroblastomas, and neurofibromas of von Recklinghausen.) Wilder Penfield (by invitation), New York City.

Abstract. The benign tumors of the nervous system arise from a specialized investment which separates nervous tissue from the rest of the body. They may be divided on histologic grounds into three groups: the meningeal fibroblastoma

(commonly called dural endothelioma), the perineurial fibroblastoma (solitary neurofibroma), and the multiple neurofibroma of von Recklinghausen's disease, although the two first named tumors are fibroblastic they are easily distinguished from each other microscopically because each retains the morphologic characteristics of the specialized connective tissue from which it arises. Only in the last group is nervous tissue to be found.

In addition to the standard methods for the study of these tumors much assistance has been gained by the use of the neuroglia and neurofibril stains of Del Rio-Hortega and of Cajal. The silver carbonate method for staining connective tissue fibers has been of particular assistance.

The type cell of the meningeal fibroblastoma is the fibroblast as pointed out by Mallory. Fibroglia fibers are formed within the tumor and when slowly growing, collagen is laid down by the neoplastic cells forming broad irregular fibers. Cell structure and arrangement resemble that of arachnoid granulations.

The perineurial fibroblastoma contains a different type of collagenous fibers. In these tumors the collagen is in the form of long slender wire-like fibers which appear in parallel. Similar slender fibers can be stained in normal nerve where they are laid down in the connective tissue. They have here frequently been confused with nerve fibers. Careful study of these tumors reveals no nervous or neuroglial elements in them. These tumors are most frequently found upon the eighth nerve and the nerve roots of the spinal cord. They are rare upon peripheral nerves.

In contradistinction to the above two tumor groups the neurofibromas are multiple tumors which appear in neurofibromatosis as an expression of a system disease which often involves a large number of nerves. Nerve fibers, derived from the nerve trunk, pass through the tumor and are surrounded by a tangle of reactionary connective tissue that is in reality a magnification of the widespread pathologic alteration of the nerves which takes place in this hereditary disease. Neuroglia cells are not found in these tumors, very rarely nerve cells may be present but they then resemble ectopic cells from a nerve root ganglion. Confusion has arisen from the fact that at times within these neurofibromas perineurial fibroblastomas may appear, possibly as a result of irritation of the perineurial connective tissue. These fibroblastomas may grow so large as to displace most of the neurofibroma tissue to the periphery. Sarcomas may likewise take their point of origin in these tumors.

In the gross also these three tumor groups have characteristic features. At operation the meningeal fibroblastoma is usually dark red, attached to the dura and often degenerated at the center. The perineurial fibroblastoma is attached to a nerve, is usually brown or yellow and degeneration, if present, takes place at a number of points resulting often in multiple small cysts with shining walls. The neurofibroma, likewise attached to a nerve, is more colorless, less vascular and on cross-section the degeneration which may take place is jelly-like and translucent. Fat granular cells are absent or infrequent in neurofibromas but common in degenerative areas of perineurial fibroblastomas.

Discussion

(Dr. James Ewing, New York.) Did Dr. Penfield state exactly what was the nature of those cells?

(Dr. S. B. Wolbach, Boston.) I would like to say that I cannot be quite satisfied with Dr. Penfield's interpretations. I have studied a great number of these

tumors which are being more carefully studied by Dr. Percival Bailey. We have a number of meningeal tumors of rapid growth. I cannot understand if these tumors are fibroblastic in origin why none of them resembles fibromas elsewhere in the body. There are tumors of the eighth nerve which approximate in appearance the tumors of the meninges. It is sometimes impossible to tell at first glance whether we are dealing with a meningioma or a neurinoma except by consulting the sheet that comes with Dr. Cushing's specimens. I am rather reluctant to accept the conclusion that these cells in both cases are of fibroblastic origin and prefer to believe in the ganglionic crest origin as some embryologists tell us.

(Dr. H. T. Karsner, Cleveland.) Dr. Penfield's discussion of the matter is interesting and clear, but I should like to ask him about the so-called neuroma or neurinoma. I have never been satisfied that such a tumor exists without the presence of ganglion cells, which, of course, are sometimes only revealed by examination of several blocks. Does Dr. Penfield propose to eliminate the ganglioneuroma with few cells and substitute for it the perineural fibroblastoma?

(Dr. Wolbach.) I have also in the last year had an opportunity to study two neurogangliomas. A recent one was very large, extending retroperitoneally from abdomen to chest and there is no question in regard to the presence of cells of nerve origin. Here again, in this encapsulated tumor there was the histology of perineural neurofibroma together with ganglion cells and I have been of the opinion that both types of cells come from a common precursor. I hesitate to quote Dr. Bailey but I believe he holds the same idea.

(Dr. Penfield, closing.) With regard to Dr. Ewing's question about the palisading cells: They are fibroblasts. I believe the fibers that one sees between and among these cells are collagen, reticulin if you like. Those same fibers can be stained on vessels where they usually wind about more. The same fibers can also be stained elsewhere in the collagenous ribbons of which they are a differentiation or precursor. I have been unable to stain any sheath of Schwann cells upon these fibers and they have not the form of nerve fibers in the central nervous system, which are more irregular in outline. They stain with connective tissue stains.

Dr. Wolbach spoke of recurring meningeal tumors. Of course, we know the meningeal fibroblastoma can recur. Also the fact that there are other types of tumors arising from the dura, which recur, seems an objection to the term meningioma which Dr. Cushing has proposed. Meningioma would include anything, I suppose, arising from the dura or which involves the dura but which would not of necessity belong to the histologic entity meningeal fibroblastoma. I cannot answer why these tumors are not like the fibromas seen elsewhere except that the cytologic picture resembles that of arachnoid granulations from which these tumors arise. Meningeal fibroblastomas tend to invade the bone and there is a tendency for arachnoid granulations to do the same thing, which I think Dr. Wolbach has pointed out.

The perineural tumors are sometimes difficult to interpret because of a great degree of degeneration. Fibroblasts which have undergone degeneration sometimes contain nucleoli and may give a superficial resemblance to nerve cells. The ganglioneuromas are certainly at times similar in appearance to the neurofibromas, not to the perineural fibroblastomas. Both contain nerve fibers and sheaths of Schwann cells. In regard to the term neurinoma that Dr. Karsner spoke of, the name signifies that the perineural fibroblastomas contain nerve fibers which is a matter of interpretation. If they are nerve fibers and contain

neoplastic ganglion cells then the name perineural fibroblastoma is a misnomer. I have tried to show that the solitary perineural tumor does not contain nerve fibers. The occasional tumor which contains ganglion cells belongs in the group of neurofibromas.

THE EFFECT OF HIGH VOLTAGE CATHODE RAYS ON LIVING TISSUE; AN EXPERIMENTAL STUDY. V. C. Jacobson and (by invitation) K. C. Waddell, Albany, N. Y.

Abstract. Forty white rats were exposed to the rays of the new Coolidge cathode tube, the area rayed being the unshaved abdominal skin. Voltages used were 100,000, 200,000, and 350,000 at 1 milliampere, the animals being one inch from the nickel window of the tube. The rats were killed at intervals of one minute to fourteen days following the exposure. At first the white hair in the rayed area is changed to yellow. This color gradually fades and the hair falls out. Desquamation and the formation of a superficial epidermal slough takes place, the necrosis gradually deepening until it reaches and sometimes penetrates into the muscle layer. The periphery of the burn shows practically no attempt at epithelial repair at the end of fourteen days. A dose of 200,000 volts for 60 seconds or 350,000 volts for 30 seconds, applied over an area one inch in diameter does not kill although the animal goes into general muscular spasm during the raying. The intensity of the histologic changes varies directly with the voltage. The first changes are degenerations in the epithelium of the skin and its appendages but very promptly the collagen of the corium and deeper layers is fused into a glassy mass which takes a deep black stain with hematoxylin, and orange-yellow with Mallory's aniline blue. Phagocytes attack and undermine the necrotic connective tissue thus exposing to the air the deeper tissues over which epithelium has great difficulty in growing. Elastic tissue is fused with the collagen bundles. An interesting point is that the cathode electrons or rays produce their greatest effect in a depth of only 1/10 mm. regardless of the voltage, dead matter (tissue) stopping the electrons perhaps even more efficiently than living tissue. The deeper tissue changes such as edema, vascular congestion and leucocytosis may be secondary X-ray effects or the reaction of the body to the presence of necrotic tissue. Direct raying of intestine destroys its muscle wall in 30 seconds and of liver its parenchyma in a depth of 1/10 mm. The profound change in the connective tissues and its effect on epithelial regeneration is being studied further.

Discussion

(Dr. A. M. Pappenheimer, New York.) What is the effect of the cathode rays on the bone marrow?

(Dr. Jacobson, closing.) I have confined the studies at present to the skin lesions, although in two rats direct raying of the exposed tibiae produced no demonstrable immediate effects. The rats, as a whole, seem to stand terrific voltage. They would go into convulsions while being rayed but come out of them without much apparent harm. A wide experimental field has been opened up by this tube. The cathode electrons produce remarkable chemical changes in substances, for instance changing castor oil into a solid, and the effect on living tissue indicates profound chemical alterations. The cathode particles themselves can apparently accomplish things not possible by the X-ray in the voltage customarily used. X-rays have never been used in voltages of 200,000.

THE BACTERIOLOGY OF THE BLOOD OF SWINE WITH PARTICULAR REFERENCE TO THE VIRUS OF HOG CHOLERA. Paul A. Lewis, Princeton, N. J.

(*Abstract not received.*)

THE DEMONSTRATION OF BACTERIOPHAGE IN OLD STOCK CULTURES. Gordon M. Kline (by invitation), Albany, N. Y.

Abstract. Previous investigations of old stock cultures have demonstrated bacteriophage in only a small percentage of cases, possibly due to the methods employed. When the technic used in examining stool filtrates for bacteriophage was applied to stock cultures, lytic substance was observed in 14 of 21 cultures studied. Typical bacteriophage, as identified by transmissibility in series and formation of plaques, was obtained from 11 of the 14 lytic cultures: namely, one *B. coli*, one *B. typhosus*, two *B. dysenteriae Shiga* and seven *B. dysenteriae* Mt. Desert strains. Tubes and plates, inoculated with the bacteria only, over a period of a few months varied from complete lysis to "normal" growth. In some instances, duplicate tubes and plates, inoculated at the same time from the same bacterial suspensions, gave these opposite extremes. This spontaneous appearance and disappearance of bacteriophagic action in these cultures associates the lytic phenomenon with other spontaneous microbic variations. The seven *B. dysenteriae* Mt. Desert strains gave both large plaques (3 to 3.5 mm. diameter) and small plaques (about 1 mm. diameter), indicating the presence of at least two distinct lytic mechanisms characterized as inherited processes rather than as chance contaminations with foreign parasites. One of the Mt. Desert strains was fished from isolated colonies ten times over a period of five years, but this procedure failed to eliminate either the lytic property of the culture as a whole or either one of the lytic mechanisms active in the strain before colony isolation. Although d'Herelle states that, "the bacteria of contaminated strains are but slightly or not at all agglutinable by a specific antiserum," the agglutinability of the cultures containing bacteriophage was normal with only one exception.

(*No discussion.*)

THE PARTICULATE NATURE OF BACTERIOPHAGE. J. Bronfenbrenner, New York City.

Abstract. Direct, as well as indirect microscopic examination of lysed cultures of bacteria, and especially the behavior of lytic filtrates in high dilutions and their ability to cause the appearance of discrete foci of lysis in bacterial cultures on solid media have led to the generally accepted view that the active principle of transmissible lysis (bacteriophage) is present in filtrates of lysed cultures in the form of discrete particles. The uniformity of the size of these particles, as found by different investigators and by means of different methods, has in itself appeared to many to be a strong indication in favor of the conception that the particles represent the units of an autonomous organized virus, as originally suggested by d'Herelle.

However, some experiments, particularly those showing that the active principle is capable of spreading from the focus radially, independently of the multiplication of bacteria, and independently of gravity, and that the rate of its spread is conditioned by the density of the medium, seem to militate against ready acceptance of such a view. Such radial spreading could be accounted for

by a working assumption that the observed particulate distribution of phage is only apparent and is due to its ready absorption on coarser colloidal particles of the medium. That such an assumption is more valid has been suggested by our experiments in which the number of particles endowed with specific activity of phage in a given volume of a filtrate was altered, depending on changes in the degree of dispersion of colloids in the medium. Experimental data presented in this paper strengthen this conception further by showing that the particles present in filtrates of lysed cultures of bacteria and endowed with properties of the phage are not uniform in size.

When filtrates of lysed cultures (bacteriophage) are subjected to prolonged dialysis under osmotic pressure against water, the presence of the lytic agent can be detected outside the membrane only during the first few days. The residue remaining inside the membrane contains the bulk of the original lytic agent, and yet it is no longer capable of diffusing into the outer solution.

The interruption of diffusion is shown not to be due to any alteration in the permeability of the membrane. Moreover, the residue fails to diffuse through a fresh membrane of similar permeability, while the dialyzed portion of the phage passes quantitatively through a new membrane. When ultrafiltration under pressure was substituted for dialysis, the residue on the filter could be washed repeatedly with water, or with buffer solution (pH = 7.4), without giving off into the filtrate any more active agent. However, if broth (pH = 7.4) was substituted for water, a renewed diffusion of the active agent resulted.

These results are interpreted as indicating that the colloidal particles present in the lytic filtrates, and apparently endowed with properties of bacteriophage do not represent autonomous units of the active agent, but merely serve as a vehicle on which the agent is adsorbed. They vary in size within limits wide enough to permit fractionation by means of ultrafiltration.

The fact that active principle can thus be shown to be distributed in the medium in a form of particles of different size does not necessarily deny its autonomous particulate nature, since the phage can conceivably be assumed to be a pleomorphic virus. However, the fact that the addition of broth to the nonfilterable residue (presumably composed of units of the agent of larger size) allows it to pass through the membrane which held it back before the addition of broth, is contrary to such an assumption, provided, as we have shown, the permeability of the membrane was not altered by the addition of broth. Such an effect of broth might explain the occasional findings of several workers who believe they have caused spontaneous production of phage by repeated filtration of bacterial cultures, heated lytic filtrates, and even sterile broth — substrata assumed by them to be free from bacteriophage before filtration.

(*No discussion.*)

THE STUDY OF INTIMATE MECHANISM OF THE LYSIS OF BACTERIA BY BACTERIOPHAGE. J. Bronfenbrenner and (by invitation) R. S. Muckenfuss and D. M. Hetler, New York City.

Abstract. When susceptible bacteria are introduced into a tube of broth containing moderate concentrations of bacteriophage, after a brief period of initial lag, the bacteria begin to multiply without showing any visible effect of the presence of the phage beyond possibly a somewhat accelerated rate of multiplication. With the rapid growth of bacteria the broth becomes increasingly turbid, until suddenly and rapidly, the turbidity disappears as the result of the appar-

ent disintegration of bacteria which can no longer be demonstrated either by staining or by cultural methods.

A number of investigators have tried to elicit the mechanism repsonsible for this sudden disappearance. As a result, there have been recorded in the literature no less than twenty hypotheses which can be roughly separated into three main groups.

The first group of hypotheses is built up about the original hypothesis of d'Herelle, who ascribed the sudden disappearance of bacteria to bursting, due to distention incident upon the intracellular multiplication of the *Bacteriophagum intestinale*. According to this conception, the bursting of bacteria accounted, at the same time, for the disappearance of bacteria as well as for the increase in the concentration of the phage in the solution. If this hypothesis is correct, there should be no lysis without multiplication of the bacteriophage, and *vice versa* — no multiplication of bacteriophage without lysis. The opposite, however, has repeatedly been shown to occur. Under proper conditions, it is possible to obtain lysis without an increase of phage, and an increase of phage without lysis. Moreover, many investigators have failed to observe this bursting, and some state that the swelling of bacteria observed by d'Herelle is not general enough to account for the disappearance of all the bacteria, that the bulk of bacteria disappears without undergoing any visible changes in morphology, and that swollen bacteria represent the cells more or less resistant to the bacteriophage, and are dissolved very slowly or not at all.

Another group of investigators ascribes the disappearance of bacteria to autolysis. However, they have failed to show the existence of a mechanism responsible for the sudden onset and extremely rapid progress of this autolysis. Besides, thus far all chemical analyses of the cultures, after the completion of lysis, have failed to indicate any increase in protein-split products, which would be expected if bacteria had become autolysed.

The third view postulates a special type of cleavage of the bacterial cell, which breaks up without chemical disintegration of its component parts. These cellular cleavage products are endowed with an independent power of multiplication and are capable of perpetuating a similar type of cleavage in other cells of the same species. Although this view, with various minor modifications, is held by several workers, it is evident that it is very hypothetical and not amenable to experimental inquiry.

Our own attempts to follow the progress of lysis by the direct observation of fresh preparations under the microscope, as well as in stained preparations, did not bring us to any definite conclusions as to the mechanism of lysis. However, we have been able to observe more or less definite increase in the size of bacteria under the influence of the phage. The use of special staining methods showed that the cell wall of the swollen bacteria remained intact in all cases, and in no instance were we able to detect any visible indication of its rupture or bursting. On the other hand, cytoplasm showed very marked changes during swelling. It took the stain less intensely and unevenly, so that in many instances it appeared to be segmented or beaded. When such cells were photographed unstained, by means of ultra violet light illumination, the cytoplasm appeared to be of uneven density. The swollen bacteria did not stain by Congo red (vital stain), thus indicating that they probably remained alive, even when extremely distended. The extent of swelling of individual bacteria, the relative proportion of swollen bacteria, as well as the actual relation between the swelling and the lysis were very difficult to establish, because the swelling and lysis of

bacteria go on simultaneously and continuously, and at different rates in the case of different individuals. The degree of swelling of individual bacteria varies to such an extent that the results of such an analysis must, of necessity, be highly subjective, which circumstance would explain the differences of opinion expressed by different workers on this point. The actual disappearance of individual bacteria from the field of observation in the fresh preparations is so sudden and rapid that it is impossible to state with any degree of accuracy which of the bacteria have disappeared.

It occurred to us that the extent of swelling and the relation of swelling to lysis might be more definitely established if instead of attempting to follow the changes of individual bacteria, a culture were considered as a whole. If an appreciable number of cells in a culture undergoes swelling, the relative volume occupied by the solids in this culture must increase, and thus affect the viscosity of the solution. Measurements were made both by means of a capillary viscometer of Ostwald and in the torsion viscometer of du Noüy. It was found that in general the viscosity of the mixture of bacteria with a corresponding bacteriophage increases steadily up to the time when visible lysis sets in, at which time the viscosity begins to diminish, until it gradually reaches the normal level. As calculated on the basis of changes in the viscosity of the solution, at the height of swelling, bacterial bodies may occupy a volume which may be from six to twelve times as great as the original volume occupied by them. If in place of living susceptible bacteria, one employs a culture of a homologous resistant variant, or heterologous bacteria, the viscosity of the solution remains unchanged. The heated bacteriophage which is devoid of its lytic power, does not induce swelling of bacteria and does not affect the viscosity of the mixture. The fact that after lysis the viscosity reaches its original level seems to indicate that swollen bacteria must be the ones which eventually undergo lysis.

The mechanism by which swollen bacteria disintegrate, however, remains to be established. Since in the study of fresh preparations one of the difficulties in following the lysis of individual bacteria is the fact that it is not possible to predict which one of the cells will disappear, and since one's attention is divided in observing a number of cells in a field, and moreover, since the actual disappearance of the bacteria is very sudden and rapid, it has not been possible to determine what actually takes place. It occurred to us, therefore, that if the lysis were recorded cinematographically, repeated projection of the film thus obtained would permit us to single out such cells as actually underwent lysis during the period of observation, and to follow them throughout this process. This method demonstrated that bacteria apparently swell to a varying degree, and then suddenly, within less than three seconds, the outlines of the cells disappear (burst ?) and in their place there remains an amorphous residue of low refractive power. This residue in turn disappears within a short time (about one minute), leaving only a few more or less refractile granules.

This rapid melting away of the bulk of the cytoplasm, which under ordinary circumstances is supposed to consist of semisolid colloidal, highly complex material, when considered in conjunction with the changes in the density and distribution of the cytoplasm, as indicated by pictures of fresh (ultra violet light), as well as of stained swollen bacteria, suggests that it became liquefied within the cell prior to the disappearance of the cell membrane. Since such a liquefaction could be accounted for only by some enzymatic process, we were led to investigate again the question of hydrolysis occurring during lysis. It seemed to us possible that the failure of earlier attempts to detect such hydrolysis might

conceivably have been due to the fact that the material subjected to analysis consisted of culture medium too rich in various products of hydrolysis to permit the detection of a possible small increase due to the lysis of bacteria. We therefore grew bacteria in the presence of the phage on synthetic medium devoid of all protein, and under this condition we have been able to detect unmistakable evidence of an increase in amino nitrogen as a result of the lysis of bacteria.

(*No discussion.*)

TULAREMIA, HISTOPATHOLOGY OF THE LESIONS IN MAN. Edward Francis (by invitation) and G. R. Callender, Washington, D. C.

Abstract. The lesions of tularemia in man may be divided into the local lesions at the primary point of inoculation, the secondary adenopathy subsequent to a primary lesion or without any evident point of entrance and the generalized lesions throughout the parenchymatous organs. The histopathology of these lesions was presented and illustrated. The early lesions are focal necroses, such reaction being followed relatively rapidly by endothelial proliferation and fibroblastic increase. The greater the duration of the disease the more marked is the fibroblastic response of the tissue to the infection. The similarity to certain types of focal lesions of tuberculosis was stressed and differential points considered. The histologic appearances alone are not considered diagnostic and should be differentiated from tuberculosis by special stains and inoculations and verified for tularemia by the agglutination reaction. Ten cases of the disease in man formed the basis of the study, three of which were fatal.

Discussion

(Dr. M. W. Lyon, Jr., South Bend.) I rise to a point in mammalogy. Dr. Callender says there are not as many rabbits in this part of the country as where he comes from. I am willing to concede there are not as many seen in public markets as one sees in Washington, but rabbits of the genus Sylvilagus are very common animals in the northern tier of the middle central states. The form occurring there is *S. floridanus mearnsi*, while the form commonly found around Washington and Baltimore is *S. floridanus mallurus*. This difference in races of rabbits may have some bearing on the distribution of tularemia, though the climatic factor is probably more important.

(Dr. H. Zinsser, Boston.) We have recently run into a case of abortus infection, an experimental infection in a young physician. In considering the diagnosis the question arose as to what extent agglutination overlapped in the two diseases. Can you give us a little information as to the difference in the serologic diagnosis and the similarity of the two infections in man?

(Dr. Callender, closing.) With reference to Dr. Lyon's remarks — I do not know that all rabbits are susceptible nor do I know of any work that has been done along this line. All rodents so far inoculated are extremely susceptible.

I am not sufficiently familiar with infection with *B. abortus* to discuss the similarities or dissimilarities between the two diseases.

With reference to the diagnosis, patients infected with *B. abortus*, *B. melitensis*, or *B. tularense* show agglutination of all three organisms, and the titer may not be significantly higher in the disease which affects the patient. Absorption tests differentiate easily and clearly so that there is no doubt in the mind of the bacteriologist.

ADDITIONAL EXPERIMENTAL EVIDENCE OF THE INTRACELLULAR DISTRIBUTION OF TUBERCLE BACILLI. Samuel R. Haythorn, Pittsburgh, Pa.

Abstract. Suspensions of virulent tubercle bacilli and Higgin's india ink were injected regionally in guinea pigs and rabbits and the transmission of tubercles, to other parts of the body by pigment phagocytes containing tubercle bacilli, followed. From pigmented subcutaneous tubercles in the groin, pigment cells bearing tubercle bacilli were traced to the regional lymph nodes, to the poststernal lymphatic channels, to the anterior mediastinal lymph nodes, and to foreign body granulomas produced about inert substances in various subcutaneous areas. Pigmented tubercles produced interstitially in the ears of rabbits led to secondary pigmented tubercles of the submaxillary and peribronchial lymph nodes. The evidence obtained points to lymphatic distribution as being largely intracellular. The secondary tubercles are formed in part from wandering cells and in part from multiplication of local endothelium. Evidence is presented to show that a certain amount of intracellular distribution through blood stream is probable but is less important than in the lymphatics.

Discussion

(Dr. A. B. Wadsworth, Albany.) One question I would like to ask. I did not quite understand the technic — whether the tubercle bacilli were injected after or before the ink.

(Dr. Haythorn.) Mixed with the ink.

(Dr. Wadsworth.) I should like to ask Dr. Haythorn if he has any information as to whether or not the phagocytosis of the ink preceded or followed the phagocytosis of the tubercle bacilli in this experiment. I am much interested in the effect of the ingestion of the ink particles on the metabolic and other cellular activities and thought you might have some interesting observations in regard to the phagocytic activity of the cells that are full of ink.

(Dr. Haythorn.) The India ink cell is capable of taking tubercle bacilli.

(Dr. Wadsworth.) When well filled?

(Dr. Haythorn.) Yes.

(Dr. Wadsworth.) Was there absolutely no relationship between the phagocytosis of the tubercle bacillus and that of the ink?

(Dr. Haythorn.) I think a phagocyte is capable of taking up either and the presence of one does not interfere with the taking of the other. I know the presence of the pigment does not interfere with the taking up of the tubercle bacilli.

(Dr. H. Zinsser, Boston.) In connection with one point I have been interested — about the idea that the first contact of the tubercle bacillus was really with the phagocytes. Polymorphonuclears might carry it.

(Dr. Haythorn.) Dr. Gardner has done more work on that than I. As he is present, perhaps he will answer.

(Dr. L. U. Gardner, Saranac Lake, N.Y.) I have made a particular study of this problem in the peritoneal cavity of guinea pigs. Bacilli were found within eosinophils during the first half hour after inoculation. From one to four hours many were phagocytized by neutrophilic polynuclears and some by mononuclear leucocytes. By twenty-four hours practically all of the bacilli were found within mononuclear cells. I do not think phagocytosis by eosinophils is general as I have found it in no other animal except the guinea pig.

In highly allergic human beings acute inflammatory exudates are often seen which are composed largely of polynuclear leucocytes. Tubercle bacilli are sometimes very abundant within these cells. As examples may be mentioned certain phases of tuberculous meningitis, and acute tuberculous bronchopneumonia.

(Dr. Haythorn.) During the early stages the tubercle bacilli were only found in the large mononuclears but there is a stage in which the polymorphonuclears were very active during the caseation of the tubercle. I have not found any polymorphonuclear leucocytes carrying tubercle bacilli but I do not consider my experiments conclusive on that point.

(Dr. H. H. Permar, Pittsburgh.) The reason that Dr. Gardner did not hear the question at first was because we were discussing the reaction about the lycopodium spores. Was the reason the tubercles did not form around the lycopodium spores because the cells which had phagocytized tubercle bacilli did not move so rapidly as those which contained only carbon pigment?

(Dr. Haythorn, closing.) You put carbon pigment and tubercle bacilli into the groin and the large mononuclears take up a great deal of the pigment rapidly but there is still pigment which is not taken up immediately, and that is left free when the tubercle begins to form. The pigment cells included in the formation of tubercle are held together in the little granulomatous mass during development. There are usually some pigment cells in the surrounding tissue not included in the tubercle. When I waited for from fourteen to seventeen days and put in lycopodium I got tubercles formed by pigmented cells containing tubercle bacilli which I believe were freed by the breaking down of the nodules. At times I put in a little lycopodium. If I was too early I got only the pigment cells not at that time included in the formation of the tubercle, but after caseation I got tubercles formed by the pigment cells presumably freed by breaking down the tuberculous nodule.

PULMONARY BLASTOMYCOSIS; ITS SIMILARITY TO TUBERCULOSIS. REPORT OF TWO CASES. E. M. Medlar, Madison, Wis.

Abstract. The two cases upon which this report is based are cases of primary pulmonary blastomycosis. Skin lesions did not precede the pulmonary manifestations. Case I was a young male aged 17 years. He died of the infection about eleven months after the onset of the disease. He had generalized infection with many joints and bones involved. This case represents the acute type of blastomycotic infection.

Case II was a male age 65 who died from cardiac decompensation. He gave no history of pulmonary or skin lesions suggestive of either blastomycosis or tuberculosis. Necropsy showed pulmonary lesions indistinguishable from old tuberculous lesions.

On microscopic study no essential difference in the histopathologic lesions could be determined if the acute phase of the tuberculous lesion was compared with the acute blastomycotic lesion or if the chronic phases of the two diseases were compared. In other words, when the virulence of the infectious agent is considered the lesions produced in these two diseases are indistinguishable. Giant cell formation appears to be brought about in the same way. Caseation appears to be produced in the same manner.

From this study it appears that the reaction to the tubercle bacillus is not specific. A similar pathologic reaction occurs in blastomycosis.

Discussion

(Dr. L. W. Famulener, New York.) I would like to ask what culture medium and the age of the culture medium.

(Dr. Medlar.) I was not particularly interested in cultivating the organism but I found Sabouraud's medium best. I also found that factors such as moisture apparently govern the production of the aerial hyphae and fruiting bodies.

(Dr. Hans Zinsser, Boston.) You did not mean to say, Dr. Medlar, that you thought there was any danger of a pathologist confusing the two conditions.

(Dr. Medlar.) I do not see how you can make the diagnosis unless blastomycetes were present.

(Dr. Zinsser.) It seemed to me in our own studies that there was considerable difference — the diffuseness and the characteristics of the giant cells. I wondered if you thought that a competent pathologist might make a mistake.

(Dr. Medlar, closing.) In fact, most cases of blastomycosis resemble more an acute type of infection. Our first case was one in which the individual had a generalized blastomycosis which had lasted from a few months to a year. Our second case was one in which we had no idea how long the infection had existed. It shows a much more typical tuberculous picture histologically than the acute case. Without the presence of blastomycetes in this last case I could not tell the difference histologically between blastomycosis and tuberculosis.

COCCIDIOIDAL MENINGITIS: G. Y. Rusk and (by invitation) L. W. Buck, San Francisco, Cal.

Abstract. A report of four cases of basilar meningitis due to the above organism. History suggestive of pulmonary infection in two cases. In these, however, all pulmonary symptoms subsided and in one case which came to complete necropsy no infection was found outside of the central nervous system, except one possible collapsed organism in a section of lung. The cases ran a course of chronic hydrocephalus or other form of intercranial pressure, at times suggesting tuberculous meningitis, brain tumor, or hydrocephalus. Operative procedures were instituted in all cases. Demonstration of the material showing the characteristic organism.

(*No discussion.*)

SOME POINTS ON THE MECHANISM OF FILTRATION BY THE SPLEEN. W. L. Robinson, Toronto, Can.

Abstract. The histologic structure of the spleen, with its arterio-capillary system opening out into the pulp sinuses to bring the blood into direct contact with the vast network of reticulo-endothelial cells comprising the pulp, would seem to have as one of its purposes that of filtration.

Filtration experiments were done by intravenous injections and perfusions of fresh isolated spleens. As substances for filtration, India ink, acid and basic dyes, colloidal solutions of copper, platinum and silver, bacterial suspensions and red cells stained with eosin, were tried.

The capillary walls as they pass through the ellipsoids and continue on to open out into the pulp are permeable for fluids, colloidal solutions and suspensions of fine particulate matter. The red cells, as has been suggested before, apparently pass on through the end capillaries into the Ampulla of Thoma and the pulp sinuses. This serves as a mechanism for separating the plasma with its foreign material from the red cells.

Small quantities of India ink solution injected intravenously were practically all filtered out by the ellipsoids. Beyond the ellipsoids the first trace of India ink adherent to the pulp cells was found about the malpighian follicles.

Freshly isolated spleens perfused first with a 2 per cent solution of potassium cyanide filtered the India ink just as readily as the living spleen in intravenous injections. The process of filtration does not appear to be a vital one.

The pulp cells even when the pulp spaces were expanded to their capacity by the perfusing fluid, quite readily filtered the minute particles of India ink. The process of filtration is not, essentially, mechanical in nature.

In all cases the fine particles of foreign material were found firmly adherent to the filamentous processes of the pulp or ellipsoid cells and could not be dislodged by the blood plasma or the perfusing fluids. That the process might be one of adsorption is suggested by the fact that while India ink and platinum and silver colloidal solutions all carrying negative electrical charges were readily filtered out both in intravenous injections and perfusions of the isolated spleen, the copper colloidal solution which carries a positive charge apparently passed through the splenic pulp without filtration.

(*No discussion.*)

THE SPLEEN IN WEST AFRICAN YELLOW FEVER. Oskar Klotz and (by invitation) Winifred Simpson, Toronto, Can.

Abstract. Very little attention has in the past been given to the changes which occur in the spleen in yellow fever. The studies in the pathology of the disease have centered upon the lesions of degeneration which are particularly prominent in the liver and kidney, but which also affect the heart. One of the prominent characteristics in yellow fever is the lack of inflammatory reactions in any of the organs. The disease is one in which a toxemia severely injures and induces necroses which are commonly preceded by a fatty degeneration.

In a study of the spleen it was found that there was a fairly constant change to be observed in the fatal cases. The malpighian bodies show a marked disappearance of their lymphoid elements, while the endothelial cells within them appear more numerous. In the early stages of the reaction the germinal centers of the malpighian bodies may show some hyperplasia of their endothelial cells which is soon followed by a hyaline degeneration and necrosis. The lymphoid follicles tend to disappear and in their peripheral portions the endothelial cells in the sinusoids become free. These cells tend to enlarge and form irregular multinucleate masses. During the degeneration of these endothelial cells the chromatin of the nuclei becomes scattered through the cytoplasm and not infrequently resembles protozoan parasites. In the pulp spaces at some distance from the lymphoid follicles the tissues are injured but no definite hyperplasia of the cells of the reticulo-endothelial system can be made out. In those cases where the spleen has been severely affected, débris arising from the dead endothelial cells can be discerned in the sinusoids.

The reaction, although not a specific one for yellow fever, assists in making a differential diagnosis from other diseases which in the tropics may simulate it. It is distinctive from that which arises in relapsing fever and infectious jaundice.

Discussion

(Dr. J. Ewing, New York.) The splenic lesion which Dr. Klotz has so minutely described reminds me of the splenic lesions one sees in cases of intestinal intoxication. I am surprised too that one should discuss yellow fever without reference to leptospira.

(Dr. A. B. Wadsworth, Albany.) I would like to ask about hemorrhagic lesions.

(Dr. S. B. Wolbach, Boston.) I should like to know whether he succeeded in transmitting this form to guinea pigs.

(Dr. H. Zinsser, Boston.) Does anyone else wish to ask another question or the same question in another form? I will ask Dr. Klotz if he wishes to answer.

(Dr. Klotz.) The work which was carried out during the past year by the Yellow Fever Commission is not completed, and further studies are to be carried on during this and succeeding years. Hence the findings which have been reported to the present can only be considered in conjunction with those which are to follow. In answer to Dr. Wadsworth's question as to the presence of hemorrhagic lesions, it was noted that these were present in petechial or small blotchy areas in the skin, lungs, stomach, intestines and serosal surfaces, but their distribution and extent were very variable. We were unable to demonstrate leptospira in the tissues obtained at necropsy.

(Dr. Wolbach.) Was transmission to guinea pigs absolutely negative?

(Dr. Klotz, closing.) The laboratory work in bacteriology and immunology was carried out by Dr. Henry Muller who was in charge of the laboratories of the Commission, and Dr. Kligler. Guinea pigs were found not to be susceptible to infection by inoculation of blood from cases of West African Yellow Fever, and to the present no leptospira was isolated on culture media. The British officers both in Nigeria and the Gold Coast were most cordial in their coöperation, and gave every facility to carry on the work.

HISTOLOGICAL AND CHEMICAL OBSERVATIONS UPON THE ORIGIN OF THE POLYCYSTIC LIVER. Ernest Scott (by invitation), Columbus, O.

Abstract. From a review of previously reported cases and three cases observed in this laboratory, histologic investigation shows that polycystic liver is a condition associated with an increase in the periportal bile ducts. Previous investigators have attributed this increase to inflammation, neoplastic growth and congenital anomaly. From investigations of the three cases in this laboratory it is our opinion that the fundamental lesion is an inflammation in the nature of a periportal cirrhosis. Since all three of the cases reported were in adults, it is impossible to say if this statement holds for the embryonic type of polycystic liver. Physical chemical determinations on the cyst fluid reveals the absence of bile and proves beyond question that the cyst fluid is the product of selective secretory activity.

(*No discussion.*)

THE ETIOLOGIC STUDY OF THE PATHOLOGY OF EIGHTEEN CONGENITAL POLYCYSTIC KIDNEYS. James E. Davis, Detroit, Mich.

Abstract. The material studied was from subjects varying from fetal life to 65 years, one at five months, one at seven and one-half months, four at term, one

a day old, one adult 22 years of age, another 32, six between 40 and 50, three at 45, 55 and 65 years of age, respectively; two were from the negro race.

There were other multiple deformations in 50 per cent of the cases.

There was definite history of inheritance in 55 per cent of the cases. In two generations there were ten instances of congenital polycystic kidneys and three specimens were obtained from one family. Three of the cases were operated upon and only one has survived operation for a period of two and one-half years after her nephrectomy.

The material showed in all instances developmental defects in both cortex and medulla, the earliest formation occurring quite uniformly in the subcortical zones in kidneys, and in certain instances in liver and spleen. In the kidneys, delayed and defective development occurred in all parts of the majority of the nephrons. Delayed development of glomeruli, convoluted tubules and collecting tubules was evident in all cases, but in addition this deficient development was always found in areas of embryonic or mesenchymal stroma.

In all instances the details of differentiation phenomena were observed from columns of unassembled mononuclear cells in mesenchymal stroma to partial assembling of these cells as straight segments with here and there partial development of lumina to advanced cystic degeneration in such areas, whether found in the straight tubules, convoluted tubules or Bowman's capsules.

Conclusion. Structural etiologic defects preceding bilateral congenital polycystic kidney degeneration are due to delayed development of entire nephronic units and their surrounding stroma.

(*No discussion.*)

A Case of Hypoglycemia, Probably Produced by a Carcinoma of the Islands of Langerhans. H. E. Robertson, Rochester, Minn.

Abstract. This is a report of the pathologic conditions found in a case of hyperinsulinism and hypoglycemia which were studied and are to be published by R. M. Wilder, F. N. Allan and H. E. Robertson.

The patient, a physician aged 40, had had pains in the upper abdomen for a long period and more recently attacks of jaundice and weakness which could be relieved or prevented by the administration of sugar, the requirements increasing until just before death when not less than 25 gm. of glucose was necessary each hour. At postmortem examination a degenerated malignant tumor was found in the tail of the pancreas with metastasis to the adjacent lymph nodes and liver. The liver and kidneys were enlarged. Microscopically the tumor cells resembled those of the islands of Langerhans in structure and arrangement. The tumor tissue in the liver was found to contain insulin. The liver showed rich deposits of glycogen. The tumor was adjudged to be a functioning carcinoma arising from the islands of Langerhans.

Discussion

(Dr. James Ewing, New York.) It looks to me like parenchyma cells, but I do not understand why the glycogen was not burned as well.

(Dr. Robertson.) I believe that the glycogen was mobilized in the liver due to the huge amounts of sugar administered. Just how that happens I am not able to say. The facts are that the patient was suffering from hypoglycemia and hyperinsulinemia and it would appear that this tumor contains an insulin-like substance.

(Dr. Maude L. Menton, Pittsburgh.) Any special stains?

(Dr. Robertson.) They did not work.

(Dr. H. T. Karsner, Cleveland.) This report is of great significance and interest. Goldblatt (*J. Cancer Research*, 1921, vi, 277) reported a case of benign adenoma of the islet tissue but found few similar cases in the literature. The diagnosis, of necessity, rested upon a presumptive identification of the type cell. Robertson has the additional evidence of a special functional capacity of the tumor to aid in its identification. This case brings to mind the old question of preservation of function of cells after they have reverted to a highly active rate of multiplication.

RIGHT-SIDED AORTA (PERSISTENCE OF THE RIGHT AORTIC ARCH). Aaron Arkin, Chicago, Ill.

(*Abstract not received.*)

COARCTATION OF AORTA (ADULT TYPE) WITH COMPLETE OBLITERATION OF DESCENDING ARCH. Maude E. Abbott, Montreal, Can.

Abstract. A case is reported of complete obliteration of the descending arch at the point of insertion of ligamentum arteriosum with persistence of the fetal isthmus and anomalous (persistent left fifth?) arch. Bicuspid aortic valve, aortic insufficiency and subaortic stenosis in a lad of 14.

The collateral circulation was extensively developed and the ascending aorta had undergone aneurysmal dilatation with dissection and impending rupture of the right anterior wall. The diagnosis was made during life on the basis of the destructive symptomatology, which is discussed in the light of the necropsy findings. The literature on rupture of the aorta in coarctation of the adult type is briefly reviewed.

(*No discussion.*)

THREE SPECIMENS OF HEARTS SHOWING CONGENITAL LESIONS. B. L. Crawford and (by invitation) Edward Weiss, Philadelphia, Pa.

(*Abstract not received.*)

REPORT OF SEVENTY-THREE CASES OF PULMONARY EMBOLISM. J. S. McCartney (by invitation), Minneapolis, Minn.

Abstract. Seventy-three cases of pulmonary embolism were found among the 9,275 necropsies on record in the Department of Pathology of the University of Minnesota. They were divided into four groups (1, *a*) post-traumatic, 15 cases; (1, *b*) post-traumatic with operation in consequence of injury, 8 cases; (2) post-operative, 31 cases; (3) postpartum, 3 cases; (4) miscellaneous, 16 cases. There were 40 males and 33 females. The age varied from 19 to 83 years. When considered in relation to the number of necropsies done in each decade, this series shows practically the same incidence of embolism in all decades after the first. Age is probably not as important a factor as it is usually thought to be.

In the postoperative group, wound infection was present in 17 cases. In 27 of the 31 postoperative cases embolism occurred during the first two weeks.

Apparently the occurrence of thrombosis and pulmonary embolism after injury is not generally well known. One hundred and nineteen cases of post-traumatic thrombosis and embolism were collected from the literature. These

together with the twenty-three reported here make a total of 142. From these 142 cases certain general conclusions are drawn. (1) Post-traumatic thrombosis and embolism are not at all rare; (2) a simple fracture was present in a majority of instances, but only rarely a compound fracture; (3) in a number of instances there was only minor bruising of the soft tissues without fracture of a bone; (4) the thrombus always developed at the site of the injury; (5) the interval between trauma and pulmonary embolism is longer than that between operation and embolism; (6) the age distribution seems to be about the same as that of other forms of pulmonary embolism; (7) injuries resulting in embolism usually involve the lower extremities.

In postoperative thrombosis and embolism the primary site of the thrombosis may lie within the operative field or be distantly removed from it. The iliac, femoral and pelvic veins are the most common sites of the primary thrombosis. The veins of the left side are most often involved. Postoperative pulmonary embolism usually follows operations below the level of the diaphragm, and only rarely those above the diaphragm, and is most common following operations on the prostate, intestine and biliary tracts.

Thrombosis and embolism develop in a great variety of medical conditions, and the thromboses are usually situated in the veins of the lower extremities, as in postoperative cases, often independent of the major anatomic lesions.

Discussion

(Dr. M. W. Lyon, Jr., South Bend.) I would like to ask if figures for simple and compound fractures have been corrected for the frequency to the one and the comparative infrequence of the other.

(Dr. McCartney.) I took all the cases here in one group without making correction for the difference in incidence of the two types. I did so for the reason that in the literature it is frequently stated that embolism is more likely to follow a compound rather than a simple fracture.

(Dr. W. W. G. Maclachlan, Pittsburgh.) In the cases which we see in Pittsburgh in the coal miners, where compound fractures are very common and often multiple, it is very rare in these severe fractures to meet with an embolism at necropsy. The few that we have seen have all occurred from minor fractures or fractures not in good position, and operated on. In the very severe injuries, and the coal miners get terrific injuries, it is rare to find embolism.

(Dr. William Boyd, Winnipeg, Can.) Is there any explanation to offer about what exactly was happening in the case where the embolism did not occur for ninety days? Has anybody come across those postoperative cases where the patient dies with all the symptoms of pulmonary embolism but necropsy fails to reveal any embolus even if done with the greatest care. We have had two or three cases of that sort.

(Dr. H. L. Jaffe, New York.) I wonder whether any evidence of embolism has been noted in those cases in which there has been no injury but just manipulation of bone or joint in a closed operation. One sees suggestive cases in orthopedic hospitals following such procedures. The patient leaves the operating room and within a few hours after going to the ward dies with symptoms like embolism and careful necropsy fails to disclose the cause of death.

(Dr. McCartney, closing.) I have not any explanation to offer at all for the long interval between the injury and the embolism. It would seem that by the

end of three months you usually should have some organization of the thrombus in the vessels. I have made no microscopic examination of any of these specimens. This is simply a statistical study of the cases, no microscopic work being done. Certainly, in our service we see every now and again cases where the clinical history indicates pulmonary embolism but we do not always find embolism. I think that is the experience of everyone. I am sure I do not know how to account for it. None of these cases followed a manipulation such as Dr. Jaffe mentioned in orthopedic hospitals. I have seen such cases in the literature and probably the explanation is the same as in the others, namely that the vein is traumatized and the intima torn.

PULMONARY ARTERIOSCLEROSIS ASSOCIATED WITH PRIMARY CARCINOMA OF THE LUNG. William Boyd, Winnipeg, Can.

Abstract. The etiology of Ayerza's disease is still obscure. Some cases appear to be due to syphilis. In others the pulmonary arteriosclerosis is associated with conditions in which there is long-continued increase of pressure in the pulmonary circulation, such as mitral stenosis, emphysema and chronic pulmonary tuberculosis. In the case described in this paper none of these factors was present, but the pulmonary arteriosclerosis was associated with carcinomatosis of both lungs. The relationship between the two conditions is discussed.

Discussion

(Dr. A. S. Giordano, South Bend.) I wonder whether or not the microscopic sections of the prostate and of the rectum were carefully searched. The gross picture of the lung is a little bit unusual for a primary carcinoma of the lung. I was wondering if there was a possibility of primary carcinoma elsewhere. I have more than once been embarrassed to find what I considered primary malignancy in the lung, not to be primary in the lung at all.

(Dr. Alfred Plaut, New York.) Would Dr. Boyd like to give an opinion as what he thinks of the causal relationship or of the coincidence?

THE INVOLVEMENT OF THE AORTIC VALVE IN SYPHILITIC AORTITIS. Otto Saphir and (by invitation) R. W. Scott, Cleveland, O.

Abstract. The most constant histologic findings of the aorta in the region of the sinus of Valsalva are endarteritis obliterans of the vasa vasorum and perivascular infiltration of lymphocytes in the adventitia. These vessel changes lead to necrosis of the media and mucoid degeneration of the inner portion of the media and intima. The degenerated areas become organized as indicated by new formation of vessels and the presence of endothelial cells, fibroblasts and young connective tissue. The perivascular infiltration about the newly formed vessels and the presence of lymphocytes throughout show that the process does not undergo healing, but proceeds continually as a chronic inflammation. Older cases show hyalinization of these areas. The constant presence of the newly formed vessels prevents ulceration. The lateral portion of the aortic valve leaflets which according to Bayne-Jones is supplied by the vasa vasorum from the aorta shows similar degenerative changes as the intima and media of the aorta. Organization of both sides leads to adhesions between the lateral portion of the valve and the aortic wall of the sinus of Valsalva leading to the gross picture of a separation of the commissure.

(*Discussed with next paper.*)

THE HEART IN SYPHILITIC AORTITIS. B. J. Clawson, Minneapolis, Minn.

Abstract. One hundred and twenty-six hearts associated with syphilitic aortitis are studied to observe the anatomic changes in the valves, coronary arteries, myocardium and pericardium, and to note the immediate relation of these changes to the cause of death.

The 126 cases on the basis of their clinical courses and the pathologic findings at necropsy are classified as follows:

1. Aortic insufficiency, 48; 36.5 per cent.
2. Sudden death from closure of coronary orifices, 25; 19.9 per cent.
3. Rupture of aortic aneurism, 35; 27.7 per cent.
4. Gummata of myocardium, 3; 2.4 per cent.
5. Miscellaneous (death from other causes), 17; 13.5 per cent.

Syphilitic valvulitis (a cord-like thickening of the free margins of the cusps) and a separation of the aortic cusps at their attachments to the aorta are commonly associated with syphilitic aortitis. The gross injury to the valve regularly produces an insufficiency but never a stenosis. Narrowing of the coronary orifices to the extent of producing death is common.

Aside from the cases with rupture of an aortic aneurism and the few cases with gummata of the myocardium, death is practically always accounted for by the aortic valvular injury with insufficiency or the narrowing of the orifices of the coronary arteries. Sudden death with syphilitic aortitis is rarely due to a myocardial inflammatory condition.

Discussion

(Dr. Otto Saphir, Cleveland.) We have noted in our cases thickening of the midportion of leaflets of the aortic valve. We do not find there any changes or any signs characteristic of syphilis. We think that the cord-like thickening of the valves is just due to chronic inflammation caused by the regurgitation of blood after the insufficiency of the valve has been established.

(Dr. W. W. G. Maclachlan, Pittsburgh.) We have been interested in the relation of the aortic valves to aortitis, chiefly through some observations in cases of aneurysm where we found, clinically, no evidence of aortic insufficiency and in others at necropsy the presence of aneurysm with normal aortic cusps. We feel that there are a certain number of aortitis cases where the process does not go much below a point about one inch above the aortic ring. We agree with the findings of Dr. Scott and Dr. Clawson that lues produces a thickening of the aortic cusps, but some cases, even advanced to degrees like aneurysm, do not appear to show this change. After the age of 50 I think one must consider the change that may occur at that time of life due to sclerosis. We have been impressed on the clinical side by the fact that students invariably interpret an aortic regurgitation in an adult as being due to lues and to aortic valve disease, and do not seem to consider that an aortitis may be present with no valvular involvement.

(Dr. R. W. Scott, Cleveland.) We are very pleased to hear that Dr. Clawson's work, which agrees in every detail with our own observations of the last seven or eight years, indicates that whether a patient having syphilis of the aorta gets signs of heart disease or not depends not upon what happens in the myocardium but whether or not the process attacks the roots of the aorta and the valves. In regard to the distortion of the architecture of the leaflets one sees an occasional

clinical picture of aortic insufficiency although at necropsy the valve is little distorted. The ring itself is dilated perhaps but has perfectly normal appearing aortic leaflets. I wonder if Dr. Clawson has observed such cases, also whether or not he has seen a syphilitic distorted aortic leaflet in which the commissure was not widened.

(Dr. Saphir.) I wonder, too, if you have found any separation of the commissure of the two leaflets without hyaline plaques above the leaflets of the aorta.

(Dr. Clawson, closing.) From the microscopic condition of the valve I regard the pathogenesis of the thickening as inflammatory in character. The amount of proliferation which I showed you on the slide had not been produced from just some other injury. This inflammatory condition starts from the aorta and is known to extend beneath the endothelium of the valve on both sides of the valve but not from the sinus of Valsalva. There are many cases of aneurism without valvular involvement but as a rule the hearts are small and the valves in many of them are not involved and there is nothing to stimulate hypertrophy. In regard to the stretching of the orifice in three of my cases the cardiac failure cannot be accounted for on a vascular basis so we figured that in these cases stretching of the aorta must have had something to do with it. Unfortunately, the width of the aorta was not measured at the time of necropsy and I thought the measurement of the formalin specimen would not be correct. I have measured the aortic ring since in typical cases of aortic insufficiency with injury to the valve and have found that the diameter of the aortic orifice was normal. I have not worked up the microscopic structure of the aorta but in regard to the hyalinized plaques above the attachment of the valve you always have a proliferation which pushes the attachment of the aortic cusps apart somewhat. At first, it may not be hyalinized but may become so later.

PERIARTERITIS OBSOLETA NODOSA. A STUDY OF THE HISTOLOGICALLY HEALED END-STAGE. Aaron Arkin, Chicago, Ill.

(*Abstract not received.*)

A BLOODLESS METHOD FOR TAKING REPEATED BLOOD PRESSURE READINGS IN LABORATORY ANIMALS. Leone McGregor (by invitation), Minneapolis, Minn.

Abstract. Investigators attempting to produce chronic arterial hypertension experimentally find it necessary to take a long series of blood pressure readings on each animal. With the method of a cannula in an artery only a few readings are possible.

My method is a combination of the procedures used by Fahr and Allen. The rabbit is tied in the dorsal position. The phonendoscope is applied over the termination of the abdominal aorta, where it may be held in place by tapes. The cuff is wound around the lower abdomen just above the iliac crests, so that the phonendoscope is just inside the lower border. As Allen has pointed out, the sounds are more clearly heard when the phonendoscope is inside the cuff than when it is distal to the cuff as in clinical procedures.

The readings are taken in the usual manner. The cuff is inflated until the aortic pulse disappears. Then the mercury is allowed to fall. The first sound which comes through is taken as the systolic pressure. With a further fall in the

mercury the sound becomes softer. This is taken as the diastolic pressure. The aortic sounds are sharp and distinct and the pressure can be read as accurately as in man. The normal aortic systolic pressure in rabbits varies from 115 to 140 mm. Hg. Adrenalin shows the same sharp rise as occurs when the pressure is measured with a cannula in the carotid. The blood pressure can be read as accurately in monkeys as in rabbits.

(*No discussion.*)

A METHOD OF PRODUCING EXPERIMENTAL CHRONIC HYPERTENSION IN THE RABBIT. A. H. Pederson (by invitation), Minneapolis, Minn.

Abstract. The kidney is approached by the posterior route. A longitudinal incision is made about one and one-half inches to the left of the mid-dorsal line, and the lumbodorsal fascia is exposed. Following the line of cleavage and separating the muscles in the direction of their fibers, the perirenal space is entered. With a little gentle pressure on the abdomen, the kidney is pushed out. The fatty capsule is stripped off and the renal vein and artery are identified and separated. An aluminum wire band is put around the renal vein, and sufficiently constricted so that the kidney becomes tense and purplish. To prevent the development of collateral circulation, the whole kidney is placed in a loose pouch of fixed animal membrane. The opening is surrounded by a purse string suture drawn about the renal pelvis and vessels. The kidney is then replaced, and the wound sutured in layers.

In the five rabbits that have survived the operation for two weeks or more, there has been a definite elevation of the aortic blood pressure, from 110 to 130 (normal) to 180 mm. Hg. or higher. The highest pressure recorded was 270 mm. Hg. The blood pressures were read by Dr. Leone McGregor by the method she has just demonstrated to you. One rabbit which has survived the operation for fifty days has a blood pressure of 180 mm. Hg. It is suggested that the hypertension is of reflex origin, due to increased resistance in the circulation through the obstructed kidney.

Discussion

(Dr. R. W. Scott, Cleveland.) I would like to ask what degree of constriction is produced by this band, and secondly, what is the nature of the material encapsulating the kidney.

(Dr. H. L. Jaffe, New York.) I would like to ask Dr. Bell if he constricted one or both veins and whether any changes in the blood followed the use of this method. Did any struggling of the animal have anything to do with the increase in blood pressure? My impression is that in rabbits blood pressure is much lower than those charts show, in the vicinity of 80 or 90.

(Dr. H. Zinsser, Boston.) I was interested in the normal blood pressure of rabbits because there has been a good deal of discussion as to arteriosclerosis present in the ordinary run of laboratory animals. There was a piece of work done not long ago about the changes in the artery due to repeated anaphylactic injury.

(Dr. E. T. Bell, Minneapolis.) Dr. Scott's question: The exact lumen of the vein was not measured but it is reduced to not more than one-sixth of its diameter and we watch it until you can just barely see the blood trickle through. The membrane is an ordinary thin paper condom. Only one vein was occluded. If you occlude both veins you get renal insufficiency and death from uremia.

Just one vein was used all the time. That produces no change in the blood chemistry. Of course you can take one kidney out and that has no effect. As to what the blood pressure is in the rabbit in the aorta: I heard a paper in the Physiology section yesterday in which blood pressures of 130 were reported in the aorta of the rat. In the rabbit by our method they were 110 to 140 as a general rule. This is a little higher than the pressure obtained with a cannula in the aorta. In discussing this with my physiological friends they thought it a little more accurate than the cannula inasmuch as we did not have to deal with the inertia of the column of mercury. Where the rabbit had a lot of arteriosclerosis in the aorta, and in many cases there was a great deal, there was no sclerosis in the small arterioles. With cholesterol feeding there is marked atheroma but that never goes beyond the large arteries.

ANALYSIS OF FOUR HUNDRED CASES OF PRIMARY HYPERTENSION. E. T. Bell, Minneapolis, Minn.

Abstract. Four hundred and twenty cases of primary hypertension that came to necropsy have been studied. Primary hypertension includes all cases with persistent or intermittent high blood pressure of unknown cause; also all cases with a heart weight of 500 gm. or more in males and 450 gm. or more in females, all known causes of cardiac hypertrophy having been excluded. In accordance with the manner of death the group may be subdivided into myocardial insufficiency, coronary disease, apoplexy, renal insufficiency and miscellaneous.

Ninety per cent of the patients were over 40 years old, and 74 per cent were over 50 years old at the time of death. In our necropsies 15 per cent of persons over 50 years of age had hypertension. The renal group are somewhat younger on the average than the rest. The proportion of males to females is about 1.4 to 1. The blood pressure tends to be highest in the group with renal insufficiency. Evidence is offered to show that all cases of idiopathic hypertrophy and dilatation of the heart with congestive heart failure are instances of primary hypertension. Gross sclerosis of the coronary arteries is more frequent and more severe in hypertensive than in non-hypertensive heart disease of corresponding age. There is some evidence that a large percentage of cases of clinical coronary disease are closely related to hypertension. It is highly probable that all cases of apoplexy on an arteriosclerotic basis belong in the hypertension group. The arteries in the parenchyma of the kidneys show some sclerosis in 97.6 per cent of cases of hypertension (severe in 61.7 per cent, slight to moderate in 35.8 per cent). The renal arterioles show sclerosis of varying degree in 88.1 per cent of all cases of hypertension. The coronary and miscellaneous groups show the lowest incidence of arteriolar sclerosis.

Discussion

(Dr. O. Saphir, Cleveland.) I would like to ask Dr. Bell if he found any fat in the arterioles of the kidneys.

(Dr. A. M. Pappenheimer, New York.) I would like to know what his ideas are on the relation of arteriosclerosis of the arterioles to arteriosclerosis in general. Is it a separate manifestation of the same thing or different altogether?

(Dr. H. T. Marshall, University, Va.) I would like to ask a question in regard to the fourteen cases in which there was no increase in the weight of the heart above the limit selected. The majority of our cases at least are accustomed to develop muscular size in proportion to the exercise but even some of the best

athletes have no muscular enlargement in spite of exercise. It may depend on family or individual peculiarity. I have often thought of that variety of pathologic condition where the adaptive hypertrophies are common. Sometimes one finds a condition of adaptive hypertrophy without increase in size. I would like to ask Dr. Bell if he thinks that increase in size of the heart would go with that number in order to prove that there was hypertension.

(Dr. Bell.) I cannot answer Dr. Pappenheimer's question as to the relation to senile arteriosclerosis. There are a great many observations to show that sclerosed peripheral arteries have no relation to high blood pressure. It is true that most diagnoses are made on clinical palpation only. We know that senile arteriosclerosis affects chiefly vessels in the extremities, the aorta and sometimes the large vessels of the circle of Willis and the larger branches of the aorta; and as far as we can judge in the cases which we studied there was no greater incidence of high blood pressure than in the normal. With disease of the small arterioles we get high blood pressure whether or not there is also senile arteriosclerosis. I do not have any definite opinion but I think the two conditions are on a different etiologic basis. I do not understand Dr. Marshall's question very accurately.

(Dr. Marshall.) I was referring not to increased heart but to the muscles of athletes. We frequently find athletes in training will show an enlargement of the muscles; after several years of training the visible muscles become markedly larger but the invisible muscles do not particularly tend to become large. This might account for the fourteen cases.

(Dr. Bell, closing.) Those cases are not proved but we must remember the blood pressures were not observed early. We cannot therefore conclude that they are cases of hypertension. There might be some other explanation.

THE ORIGIN OF THE ALVEOLAR PHAGOCYTE STUDIED IN PARAFFIN SECTIONS OF TISSUE STAINED SUPRAVITALLY WITH NEUTRAL RED. Leroy U. Gardner and (by invitation) David T. Smith, Saranac Lake, N. Y.

Abstract. A new method has been devised to preserve supravital staining with neutral red in paraffin sections. Animals are killed by air embolism and the dye is introduced either into the air spaces through the trachea or into the vascular system. This technic has been employed to study the histogenesis of the alveolar phagocyte.

Intravenous staining affects chiefly the cells in the framework of the lung; intratracheally it not only reacts upon these cells, but is sufficiently irritating to provoke a very rapid migration of alveolar phagocytes.

From the character of the cytoplasmic reactions to neutral red it has seemed possible to identify the alveolar phagocyte with the "septal cells" which project above the surface of the epithelium lining the air spaces. These septal cells are in turn classified as a form of clasmatocyte or connective tissue phagocyte.

From the study of this material we have concluded that the septal cells rapidly desquamate because of the presence of the irritating dye in the air spaces. The epithelial cells are not affected but remain in position. Within the alveoli the desquamated septal cells undergo morphologic and physiologic modifications resulting in the formation of typical alveolar phagocytes. New septal cells, replacing those which have migrated from the alveolar walls, are regenerated from connective tissue monocytes which in turn arise from dormant reticulum cells, stimulated by the presence of the irritating dye.

In support of these views the following observations seem pertinent:

Within five minutes after intratracheal staining the alveoli contain large numbers of phagocytes indicating a readily accessible source of supply. Such a source might conceivably be found in the following locations: (1) cells already in the alveoli; (2) cells in the circulating blood; (3) cells in the permanent structure of the lung. The first source, preëxisting alveolar cells, can be eliminated for two reasons; first, because phagocytes appear too rapidly for cell division to have taken place, and secondly, because the experiments were repeated on guinea pigs, only one day old, whose lungs not being previously irritated by inhaled dust do not contain free phagocytes. The second source, cells in the blood stream, can also be eliminated. The number of available cells remaining in the pulmonary vessels after the circulation has failed is too small to supply all of the free phagocytes which are observed. There remains, then, only some cell in the permanent structure of the lung, as a source of alveolar phagocytes.

The fixed tissue elements which have been suggested as possible origins are alveolar epithelium, capillary endothelium and connective tissue phagocytes or clasmatocytes. The reactions to neutral red of the first two types in no way resemble those of the alveolar phagocyte. Epithelial cells, studied in thick sections, exhibit only a few fine granules widely scattered throughout the cytoplasm; endothelial cells do not take up the dye at all, unless they are so damaged that the nucleus is stained. Furthermore, there is no evidence of any depletion of these cells after intra-alveolar irritation. Their number remains the same before and after intratracheal injection of neutral red.

The clasmatocytes of the connective tissue increase in number with the duration of irritation. They are apparently derived from extra vascular monocytes which are in turn produced by stimulation of dormant reticulum cells (Sabin). Clasmatocytes are found to some extent in the heavy areolar tissues of the trunks, and are very abundant in the alveolar septa. In the latter position they often project into the lumen of the air space between the epithelial cells. They are characterized by great numbers of neutral red granules, varying in size and color, scattered throughout their cytoplasm. After the dye has been injected into the trachea of the recently killed animal, the number of clasmatocytes in the alveolar septa is notably decreased. This is not so obvious in the living animal where regeneration is constantly taking place. Because of the similarity between the staining of free phagocytes and those in the connective tissues, and because of the depletion of the latter by the intratracheal injection of irritants, we favor this cell as the usual source of alveolar phagocytes.

However, it is not impossible that some of the immature connective tissue monocytes may migrate directly into the air spaces. This form, which is usually smaller than that in the blood, has been found in the alveoli, although it is rare. Its arrangement of neutral red granules in a rosette even more closely resembles that seen in the early free phagocytes than that in the cells of the septa.

Discussion

(Dr. Alfred Plaut, New York.) We have the term desquamation. All the books contain it. One speaks of desquamative pneumonia in tuberculosis and in other infections. I have never been able to find this conception compatible with the normal histology of the human lung. Our alveolar epithelium chiefly consists of extremely thin scales without nucleus and without distinct structure of the protoplasm. Smaller well structured pavement cells with nuclei are in

the minority. Therefore, it is difficult to trace the large numbers of nucleated cells which are found in the air cells of inflamed lungs to the alveolar epithelium.

(Dr. H. H. Permar, Pittsburgh.) Concerning the question of alveolar epithelium as the source of lung phagocytes, I too would be glad to hear nothing more. Some of us think we have settled that part of the problem, and I wish we might discontinue that part of the discussion. I believe one can see alveolar epithelium in certain pathologic states, tuberculosis, for instance, where there is a definite atelectatic process in the lung. We could discuss the origin of the dust cell all afternoon, but I am not yet willing to give up the endothelial origin. Dr. Gardner's stain does not stain the endothelium. I did not see, in the pictures, the capillaries in the alveolar walls. I should think you would see the nuclei of the cells lining the capillaries there.

(Dr. Gardner.) You can.

(Dr. Permar.) I did not see them in the pictures shown.

(Dr. Gardner, closing.) I might state that in the chronic organizing pneumonia so common in guinea pigs that one occasionally finds areas in which the epithelium has regenerated with the so-called fatty vacuolated type of cell. This type does not take neutral red at all. One can see connective tissue phagocytes lying behind the unstained epithelium.

DIFFUSE ADENOSIS OF VAGINA: A VERY RARE DISEASE. Alfred Plaut, New York City.

Abstract. At the age of 50 years, one year after menopause, a profuse vaginal discharge began. When the patient sought medical help two years later, a tumor-like mass protruded from the vaginal fornix. All the other pelvic organs were normal. Two small pieces were excised, and a diagnosis of adenoma of Bartholin's gland made. The tumor was considered as beginning malignancy. After several weeks the whole vagina together with the uterine cervix was amputated. The entire inside of the vagina was purple-red and showed a number of irregular eroded areas partly with central circular depression. The tissue in the eroded areas appeared granular; the underlying vaginal tissue and the paracolpium were of normal firmness and apparently not invaded by any foreign tissue. The posterior surface of the specimen was smooth.

The microscopic picture is not that of a tumor. Glandular ducts are scattered throughout the whole vagina in the connective tissue between the surface and the muscular coat. The surface epithelium is preserved at a few points only. It is normal squamous epithelium; no connection of it with glandular structures can be seen. The glands show much variation. Often large cavities are seen with smaller ones in the surroundings which obviously are parts of the larger one. Some narrow very long ones are found right under the surface. A low cylindrical epithelial cell prevails. The surrounding connective tissue is infiltrated; this accumulation of cells looks more inflammatory than like cytogenic tissue. Only a slight similarity with endometrial tissue can be noted. The tissue in the fornix is free of glandular structures. There is no connection with cervical glands and no connection with the peritoneal surface epithelium. A derivation from any embryonic remnants is highly improbable in such a diffuse lesion which in a homogenous way involves the whole vagina of an old woman. These glands look as if they had originated at the spot where one sees them now. Two such cases could be found in the literature, one with the diagnosis: diffuse adenoma of vagina, the other one called adenomatosis vaginae.

In our case the name adenosis was chosen because it does not prejudice anything and indicates that the condition is not of true neoplastic nature. No overgrowth of muscular tissue was found around the glandular ducts. Probably this disease belongs as a special form into the group of diseases the chief representative of which is the adenomyosis. Our patient was nulliparous.

Discussion

(Dr. A. S. Giordano, South Bend.) The microscopic picture resembled much the endometrial tissue in the so-called adenomyomas. Why could we not explain that on the basis of aberrant endometrium? We find aberrant thyroid in many places and why not aberrant endometrium? Certainly the glandular structure and stroma make it very suggestive of the relationship to endometrium. Going back to the history of this woman, was there curettage? The usual curettage means bleeding. I wonder if this was a type of menstruating endometrium present at that time.

(Dr. Plaut, closing.) I do not consider this tissue identical with endometrium. Endometriosis in the vagina has never been described. The glandular tissue in our case has no relation to endometrium proper. It cannot be a metastatic endometriosis. How can it be explained how it got there? If we should call it ectopic endometriosis we would have to go back to the embryonic state; it could not then be diffuse and restricted to the submucous layer.